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Aging and dark adaptation.

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AGING AND DARK ADAPTATION

by

GREGORY JACKSON

A DISSERTATION

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ABSTRACT OF DISSERTATION
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Title Aging and Dark Adaptation

A common visual problem reported by older adults is difficulty seeing under reduced illumination and at night. Alterations in dark adaptation kinetics have been suggested as a possible mechanism of decreased scotopic sensitivity. Taking into account the effect of lens density and pupil size, dark adaptation was measured in adults ranging in age from the 20s to 80s. The older subjects' retinal health was characterized by a macular grading scale. The sample consisted of 94 subjects (n[20s] = 10; n[30s] = 8; n[40s] = 10; n[50s] = 20; n[60s] = 21; n[70s] = 17; n[80s] = 8) with 20/25 visual acuity or better who were tested with dilated pupils in a modified Humphrey Field Analyzer. After exposure to a 98% bleach, dark adaptation was measured until the subjects' threshold reached within 0.3 log unit of their baseline scotopic sensitivity. Light sensitivity for a 1.7° target of 500 nm was measured at 12° in the inferior visual field along the vertical meridian. Lens density was estimated using Sample's technique. The rod-cone transition time increased with decade at a rate of 0.65 min/decade. The slope of the 2nd component of sensitivity recovery (rate of rhodopsin regeneration) decreased as a function of decade at a rate of 0.15 dB/decade. The slope of the 3rd component of dark adaptation decreased with decade at a rate of 0.05 dB/decade.

The duration of time to reach within 0.3 log unit of baseline scotopic sensitivity increased 2.76 min/decade. The baseline scotopic sensitivity of the subjects decreased as a function of decade at a rate of 0.66 dB/decade. These findings suggest that aging-related slowing of dark adaptation may, in part, be responsible for the aging-related scotopic sensitivity loss reported in the literature. Directions for future research are discussed.

DEDICATION

To Cindy, whose encouragement made this possible.

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LIST OF ABBREVIATIONS

ADVS	Activities of Daily Vision Scale
AMD	Age-Related Macular Degeneration
AREDS	Age-Related Eye Disease Study
ARM	LogMAR
DHQ	Driving Habits Questionnaire
HFA	Humphrey Field Analyzer
ETDRS	The Early Treatment of Diabetic Retinopathy Study
logMAR	log Minimum Angle Resolvable
LDI	Lens Density Index

INTRODUCTION

Aging-related night vision problems reduce the quality of life of older adults. The elderly experience more problems with nighttime activities than younger people (Kline et al., 1992). Previous research has shown that scotopic sensitivity (dark-adapted absolute threshold) declines with age; however, the mechanism of the decline is unclear. Two general hypotheses have been advanced concerning the mechanism for the aging-related decline of scotopic sensitivity. The first theory is that absolute threshold declines with age (Birren & Shock, 1950). Physiologically, this effect possibly could be produced by a lowered rhodopsin concentration or photoreceptor drop-out among other causes. The second theory is that the rate of dark adaptation decreases with age (Birren & Shock, 1950). This effect could be produced by a slowing of rhodopsin regeneration with age. A decreased rate of rhodopsin regeneration could be caused by changes in the permeability of Bruch's membrane and the retinal pigment epithelium that slow photopigment regeneration by depriving the rod outer segment of the precursors rhodopsin regeneration.

The measurement of dark adaptation has been validated as a method to measure alterations in the phototransduction pathway and rhodopsin regeneration (Lamb, 1981; Stabell, Stabell, & Fugelli, 1992). In this dissertation, dark adaptation refers to recovery of light sensitivity following bleaching of the photopigment. Alterations of dark adaptation kinetics have been found in a variety of diseases that affect phototransduction

directly, such as age-related macular degeneration (Brown, Adams, & Coletta, 1986), Sorsby's fundus dystrophy (Jacobson et al., 1995), vitamin A deficiency (Cideciyan, Pugh, Lamb, Huang, & Jacobson, 1997), or indirectly, such as cirrhosis of the liver (Haig, Hecht, & Patek, 1938).

Most authors find a decreased scotopic sensitivity in the elderly population (Birren, Bick, & Fox, 1948; Jackson, Owsley, Cordle, & Finley, in press; Luria, 1960; McFarland, Domey, Warren, & Ward, 1960; Sturr, Zhang, Taub, Hannon, & Jackowski, 1997); however, Pulos did not (1989). Birren and Shock (1950) and McFarland et al. (1960) concluded that the rate of dark adaptation did not decrease with age, but Holopigian, Seiple, Greenstein, Kim, & Carr (1997) did find an aging-related slowing in the rate of dark adaptation. Given the methodological flaws in the previous literature on dark adaptation and aging, which will be described later, it is an open question whether the rate of dark adaptation decreases with age.

In the following section, a description of dark adaptation and the typical methodology employed to measure dark adaptation is discussed. The pre-retinal factors of pupil size and lens density that complicate the measurement of dark adaptation are described. An analysis of the previous research on aging and scotopic sensitivity and dark adaptation is presented. The impact of age-related macular degeneration is discussed. Possible mechanisms of dark adaptation are reviewed. Finally, the possible functional impact of an aging-related slowing of dark adaptation is discussed.

Typical Dark Adaptation Paradigm

Dark adaptation is traditionally measured in terms of the recovery of light sensitivity by the retina in the dark following an exposure to an intense light. The paradigm described by Hecht, Haig, & Wald (1935) typifies the method employed in much of the dark adaptation literature. The subject is exposed to a pre-adapting or bleaching light for a specified amount of time. After the light is extinguished, light sensitivity is measured several times over a period of 30 to 40 min. The bleaching light desensitizes the cone and rod photoreceptors to light. The desensitization of the rod photoreceptors by the bleaching light is dependent on the intensity of the light and the duration of the exposure to the light (Hecht, Haig, & Chase, 1937; Mandelbaum, 1941; McDonald, 1940). Complete photoreceptor desensitization is desired to produce the greatest range of cone and rod response. Light sensitivity during dark adaptation is wavelength and eccentricity dependent (Hecht et al., 1935). The wavelength and location of the stimulus are selected to maximize the response of the rod photoreceptor system because rods are responsible for scotopic vision.

The dark adaptation curve is produced by plotting the log of the thresholds as a function of time (Figure 1). The observed dark adaptation curve is a biphasic function composed of two overlapping exponential functions. The first and faster phase of dark adaptation represents the cone-mediated contribution. The slower and longer second phase of the dark adaptation function is the rod-mediated contribution. The inflection point between the two phases represents the rod-cone break. The rod-cone break

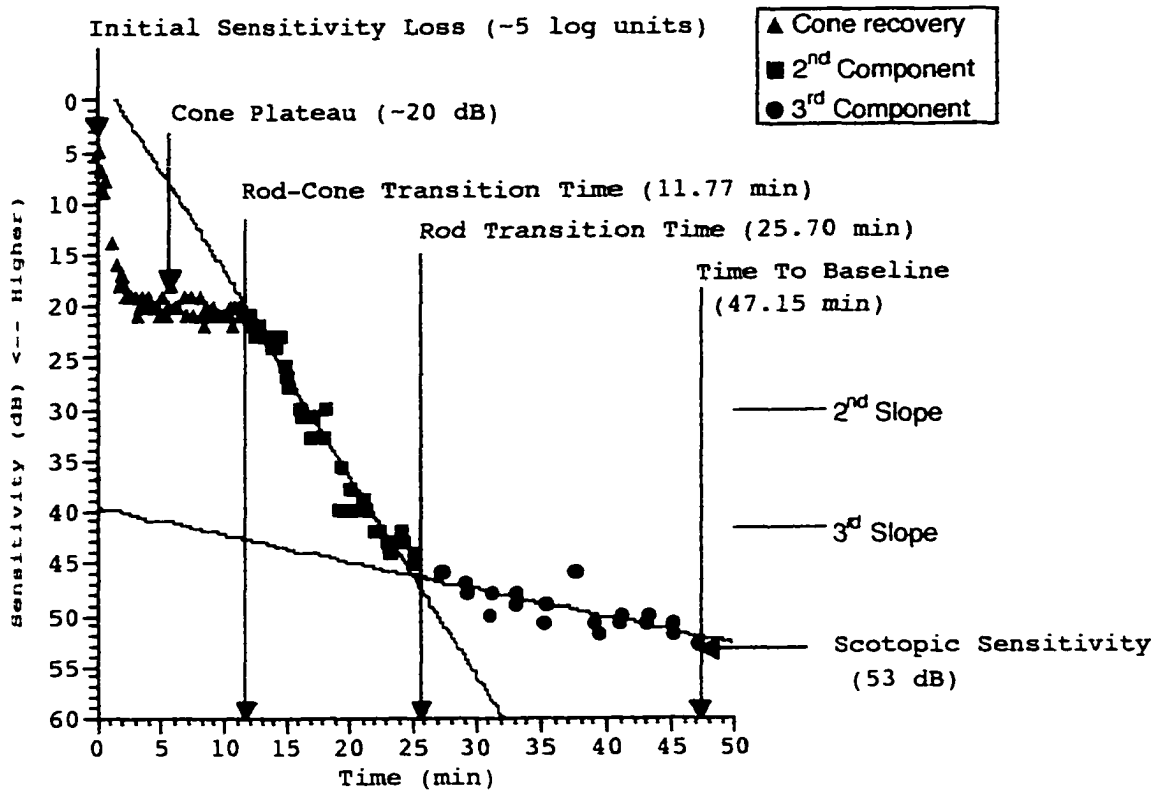

Figure 1. Typical dark adaptation curve of human observer. This dark adaptation curve is from a 25-year-old person with normal vision. The parameters of interest are the rod-cone transition time, rod transition time, 2nd slope, 3rd slope, time to baseline, and scotopic sensitivity.

represents the point in time during dark adaptation that the recovering rods' sensitivity surpasses the cones' sensitivity.

Effect of Age-Related Optical Changes on Dark Adaptation

The study of aging and dark adaptation has been complicated by the existence of two pre-retinal factors that change with age, pupil size and lens density. Average pupil diameter in the dark declines with age (Kadlecova, Peleska, & Vasco, 1958; Loewenfeld, 1979). The effect of this pupil size constriction is to reduce the amount of light reaching the retina in the elderly eye. During the dynamic process of dark adaptation, Woodhouse and Campbell (1975) found that subjects with dilated pupils obtained a sensitivity 10 times greater than subjects with natural pupils. Thus, if natural pupils are employed in aging research, the elderly subjects' light sensitivity during the early part of the dark adaptation curve is depressed in large part because of the slowed dilation of the pupil in the dark compared with the younger adults' pupils. Additionally, the final dark-adapted sensitivity would be depressed because of constricted pupil size compared with that of younger subjects. Sloan (1940) measured the effect of pupil size on the measurement of scotopic sensitivity. Results indicated that a subject with a pupil diameter of 3.0 mm would have a threshold 0.45 log units lower compared with the threshold with a pupil diameter of 5.0 mm. If the pupil diameter is 5.0 mm or greater, threshold correction for pupil size is insignificant. Dilation of the pupil to a diameter greater than 5.0 mm is an effective way to control for the effect of a constricted pupil on light sensitivity. The pupil diameter should be measured in the dark to ensure adequate dilation was achieved.

Like decreased pupil size, lens density is a source of light loss to the retina in the older eye. Lens density acts primarily to absorb light before it reaches the retina. Even in young eyes, there is absorption of light by the lens (Norren & Vos, 1974). For the average observer under 60 years old, lens density at 400 nm increases at a rate of about 0.12 density unit/decade. After age 60, lens density increases at a rate of about 0.4 density unit/decade (Pokorny, Smith, & Lutze, 1987). The absorption of light by the lens is wavelength dependent (Said & Weale, 1959). For wavelengths of light over 700 nm, absorption of light by the lens is insignificant. The greatest absorption of light occurs at 430 nm. Previous studies on dark adaptation and aging did not control for the effect of lens density (Birren & Shock, 1950; Holopigian et al., 1997; McFarland et al., 1960). Thresholds can be corrected for the effect of lens density by using Said and Weale's data (Said & Weale, 1959). A drawback to this correction is that it is based on group averages and does not consider individual differences in lens density among subjects, which are known to be highly variable (Sample, Esterson, Weinreb, & Boynton, 1988). For this dissertation, a perimeter-based estimate of lens density developed by Sample et al. (1988) was used to individually estimate each subjects' lens opacity. The rationale and method of the lens density index are presented below. The estimated amount of light absorbed by the lens is subtracted from the threshold. Because lens density is individually determined for each subject, this correction may be more accurate than a generalized correction.

Previous Research on Dark Adaptation and Aging

The effect of aging on dark adaptation was first of interest as researchers attempted to define the normal range of dark adaptation to aid in the diagnosis of vitamin A deficiency, but these studies did not have a large number of older subjects (Haig et al., 1938; Hecht & Mandelbaum, 1939; Luria, 1960; Steven, 1946). Although there was an awareness of the effects of pupil size and the absorption of the ocular media on dark adaptation, very few of the early studies controlled for these optical effects. As mentioned earlier, age-related decreases in pupil size and increases in absorption of the ocular media serve to place the elderly at a disadvantage because less light is reaching the retina. However, the historical value of this early literature is that it established that older adults tend to exhibit decreased scotopic sensitivity although the cause of that loss is unclear.

Hecht and Mandelbaum (1939) mentioned only in passing that older subjects exhibited a decrease in scotopic sensitivity to a 3° violet light located 7° in the nasal visual field compared with younger subjects. However, they provided no further details on this result. Stewart (1941) examined the effect of aging on dark adaptation. With increased age, the final dark-adapted threshold was elevated significantly. A significant slowing of the rate of dark adaptation with age was found. Stewart used a different paradigm than the classic methodology. The target was a letter "E" positioned in different orientations. The letter was illuminated with a constant white light. When the subject responded that the letter was visible and correctly identified its orientation, the time was recorded. This

task requires both recovery of light sensitivity and acuity. Nine light levels were used, each corresponding to half of the previously used light intensity. The lowest light level at which the subject correctly identified the orientation of the letter and the time required to reach each light level was of interest. The subjects were light adapted to a constant light for 15 min before dark adaptation was measured. The slowing of dark adaptation was revealed because the majority of the oldest group (over 60 years old) took longer than 45 min to reach the lowest light level presented. Very few of the subjects in their 20s to 30s exhibiting this delay. This report was statistically barren; however, it typifies much of the early work. Although Stewart commented that fatigue and pupil size appeared to contribute significantly to a subject's ability to dark adapt, no effort was made to control for these variables. An increase in the variability of the thresholds with age was found and reflects a frequently reported general trend in the aging and vision literature.

In an effort to determine the normal range of scotopic sensitivity for the human observer, Robertson and Yudkin (1944) examined whether age should be included as a factor that affected on scotopic sensitivity following dark adaptation. A total of 758 factory workers participated as subjects. The age range was 14 to 71 years old. Only 7 people in the sample were over 65 years old. There was no report of the visual health of the subjects, no correction for the effects of the ocular media, and no measurement of pupil size. Subjects adjusted to the dark for 35 to 40 min before scotopic sensitivity was measured. Thresholds were measured with a Crookes' adaptometer as described by Yudkin (1941). The target was an arrow of differing orientations that subtended an angle of 6 degrees on the retina. To screen large numbers of subjects, the minimum amount of

light needed for the subject to detect the target was recorded for about 2 min. resulting in about five thresholds for each subject.

Robertson and Yudkin (1944) reported a significant decrease in older adults' scotopic sensitivity. Adults over the age of 50 exhibited an average sensitivity loss of about 0.4 log unit compared with subjects in their 20s. Of significance. Robertson and Yudkin attributed the decrease in scotopic sensitivity to the age-related decline in pupil size. Thus, a tentative first hypothesis for age-related scotopic sensitivity loss was tested in the following manner. A post hoc correction for pupil size was applied to the data correcting for the loss of light reaching the retina. This correction did not allow for any other age-related changes such as absorption of light by the ocular media. As the basis for the correction, they used mean scotopic pupil sizes for various ages. After correcting the thresholds. Robertson and Yudkin interpreted their data to suggest that pupil size accounted for the scotopic sensitivity loss found in older subjects. Further. they concluded that age-related changes in the ocular media and retina would not be necessary to explain the decreased scotopic sensitivity in the older subjects. Later work on this issue did not support the idea that an age-related decline in pupil size was the primary mechanism of age-related scotopic sensitivity loss. Because of increasing individual differences found with age. Robertson and Yudkin suggested taking age into account in the definition of normal scotopic sensitivity.

Steven (1946) acknowledged that senile changes occur in the ocular media. He stated that no satisfactory method of dealing with these progressive changes was available. Steven's study controlled for pupil size. The actual scotopic pupil size was

measured, and the subjects' thresholds were standardized to 5.0 mm. This allows for individual correction of thresholds based on each subject's individual pupil size. Besides increased elegance of design, measuring the individual pupil size takes into account individual differences. As mentioned, pupil size in the dark decreases with age, but the amount varies by individual. Unfortunately, Steven reported no visual health information, other than to say that subjects with night blindness were excluded.

In this study, Steven (1946) measured the scotopic sensitivity of 628 subjects. The subjects were grouped by decade from 10 years and younger to age 51 and over. The oldest group contained only 20 people with a mean age of 54.4 years old; thus, this study does not address visual function in the "oldest old." The subjects were tested on a portable dark adaptometer described by Wald (1941). The target was a circular spot of light that subtended 2.4° of visual angle and was located 6° below a red fixation light. Threshold was determined by increasing the light intensity of the target until the subject reported seeing the target light. The wavelength of the target was not specified, implying it might have been white light, but this cannot be determined.

Results (Steven, 1946) indicated that an average of 0.05 log units of sensitivity was lost compared with the previous decade until age 40. The over-51-year-old group had a decline of 0.17 log units compared with the previous decade. Steven acknowledged that the smaller number of subjects in the older age group prevented a more detailed analysis. The oldest group exhibited a scotopic sensitivity decline of 0.39 log units compared with the subjects in their 20s. Steven noted an increase in individual differences for those subjects over 40 years old, as did earlier reports. Consequently, Steven

concluded that detecting pathology by use of dark adaptation would be difficult for older subjects. Because pupil diameter was controlled in this study, Steven's data refutes the notion that age-related pupillary changes are the sole cause of the age-related decreases of scotopic sensitivity found in older adults.

Birren et al. (1948) sought to correct some of the previously outlined shortcomings of the literature by attempting to control both pupil diameter and the contribution of the lens. They tested a large sample of older adults rather than only sparsely recruiting subjects in late adulthood. Earlier studies examined factory workers that would have effectively excluded elderly adults who experienced age-related declines and could no longer work. Because the prevalence of ocular pathology increases with age, the earlier studies by Robertson and Yudkin (1944) and Steven (1946) attempted to exclude elderly adults with ocular pathology by testing only working adults. Birren et al. (1948) wanted to test a truly representative sample of the elderly, so they tested unemployed subjects as well as employed subjects.

The sample included 130 male subjects between 18 and 83 years old (Birren et al., 1948). The subjects' light sensitivity was measured with a Hecht-Schlaer adaptometer. The stimulus was a 3° light (< 460 nm). The stimulus was presented 7.5° from fixation in the nasal visual field. After 3 min of light adaptation to a 11.68 log μμL field, light sensitivity was measured every min for the first 10 min, then every 2 min until 30 min elapsed. A subset of the population was tested with both violet and white light to determine the influence of violet light on the final threshold. This was the first attempt in the literature to determine whether age-related changes were wavelength dependent. A

large disparity between the violet and white light thresholds may indicate increased absorption by the ocular media because there is greater absorption of short wavelength light by the lens. Of note, all subjects over 40 were dilated to avoid the effects of senile miosis. If all subjects dilated to a diameter over 5.0 mm, the threshold correction for pupil size is minimal or insignificant. However, without individual measurement of the subject's pupil size, the need for correction or the amount of correction is uncertain because some individuals are less responsive to dilation than others.

Results (Birren et al., 1948) indicated that final dark-adapted sensitivity decreased with increased age. Older adults (70 to 90 years old) exhibited a final dark-adapted sensitivity decline of 1.24 log μμL compared with younger subjects (18-29 years old). The range of individual differences was found to increase with age. The final dark-adapted thresholds for the white light were not significantly greater for the younger group compared with the older group, suggesting that, in this sample, absorption by the ocular media was only slightly different. Overall, the use of violet light decreased sensitivity by only 0.15 log μμL. Birren et al. expected a larger difference in threshold between the two wavelengths if lens density was the mechanism underlying the old adults' scotopic sensitivity loss. The institutionalized and noninstitutionalized did not differ significantly in regards to their light sensitivity.

Birren and Shock (1950) examined the effect of aging on the rate of dark adaptation. One theory they considered was that age-related changes in scotopic sensitivity were caused by a change in the rate of dark adaptation. This hypothesis suggests that older adults have the same scotopic sensitivity as younger adults but take a

longer period of time to adapt to that sensitivity. This proposed decrease in rate was thought to be caused by slowed photopigment regeneration. Slowing of photopigment regeneration would manifest itself as depressed light sensitivity of the older observer compared with the young subject for equal times of dark adaptation. It was known at the time that vitamin A deficiency disrupted the photopigment regeneration pathway and produced a slowed rate of dark adaptation (Hecht & Mandelbaum, 1939). Birren and Shock were the first study to report both the absolute threshold and the rate of adaptation in the same subjects. The rate of dark adaptation was quantified as the rod-cone break. For example, a slowed rate of dark adaptation would indicate a longer rod-cone break. Of note, dilation and the measurement of pupil size were employed to control for the effect of pupil size on the light thresholds. Absorption of light by the ocular media was not considered, typical of the early work.

Ninety-one male subjects from 40 to 83 years old participated in Birren and Shock's (1950) study. Elderly subjects were well represented because 41 men over the age of 70 years were tested. All of the subjects' pupils were dilated, and the thresholds were corrected to that of a 5.0-mm pupil size. The subjects' light sensitivity was measured with a Hecht-Schlaer adaptometer. The target was a 3° violet light (< 460 nm). The stimulus was presented 7.5° from fixation in the nasal visual field. After 3 min of light adaptation to a 498 μμL field, light sensitivity was measured every min for the first 10 min, then every 2 min until 30 min elapsed.

Birren and Shock (1950) found little evidence that the rate of dark adaptation differed with age. Small increases in the rod-cone break were found for the older subjects.

However, this was deemed insignificant because of the increasing individual differences found in the elderly subjects. There was no association between age and the rates of cone and rod adaptation. The final dark-adapted sensitivity did significantly correlate with age. Final dark-adapted sensitivity declined with age. At 26 min of dark adaptation, the threshold of the 70- to 83-year-old group was about 0.76 log units greater than the 40- to 59-year-old group. A similar threshold elevation of about 0.78 log units was found at 6 min of dark adaptation. The fact that the sensitivity difference remained fairly constant during dark adaptation points to the effect of lens density.

Birren and Shock's (1950) work confirmed previous findings that older adults exhibit a decreased scotopic sensitivity compared with younger adults. Furthermore, they concluded that the primary cause of the age-related decline in dark adaptation is a general decrease in light sensitivity and not a decrease in the rate of dark adaptation. Although the study rules out the effect of pupil size, the generalized decrease could be because of either absorption of the ocular media or some unidentified biological process.

The most quoted psychophysical work on dark adaptation and aging is from the laboratory of McFarland (Domey, McFarland, & Chadwick, 1960; McFarland et al., 1960; McFarland & Fischer, 1955). McFarland et al. (1960) studied a large and socioeconomically diverse sample of subjects. They believed a larger sample was necessary to generalize to the general population, considering the previous findings that individual differences increased with age. Despite its frequent citation in the aging and vision literature, the lack of correction for pupil size or absorption of the ocular media severely limits the usefulness of the data.

McFarland et al.'s (1960) study included a large sample of 240 male subjects from 16 to 89 years old. Eye exams were administered to only half of the participants. No characterization of the subjects' visual health was published. The subjects' light sensitivity was measured with a Hecht-Schlaer adaptometer. A 1° violet (405 nm) stimulus was used. After a 3-min exposure to a 1600 mL adapting field, the subjects fixated on a red fixation point 7° right of center. Thresholds were measured for 40 min. For the first 10 min, the threshold was measured every 2 min. The remainder of the thresholds was measured every 3 min.

McFarland et al.'s (1960) results indicated that the final dark-adapted sensitivity decreased with age. The subjects were grouped by decade, and their dark adaptation functions were averaged. From curve fitting, the rod-cone break was found to be 5 to 6 min and did not increase with age. Based on the comparison of the rod-cone breaks, it was concluded that the rate of dark adaptation did not decrease with age. The oldest group compared with the youngest group exhibited a final dark-adapted sensitivity loss of 2.4 log units; that is almost three times as great as typically reported in the literature (Birren et al., 1948; Gunkel & Gouras, 1963; Jackson et al., in press; Sturr et al., 1997). The same comparison made with the initial threshold produced a sensitivity loss of 0.69 log units. After 40 min of dark adaptation, elderly subjects had not reached the light sensitivity that the young subjects obtained after 6.0 to 7.0 min of adaptation.

McFarland et al.'s (1960) study is consistent with the hypothesis that older adults' decline in scotopic sensitivity is not caused by a decreased rate of dark adaptation. The mechanism of the scotopic sensitivity decline is obscured in this study

because of the lack of appropriate controls for pupil size and lens density. From a functional perspective, this study implies that lowered scotopic sensitivity could produce functional differences in time-limited tasks. Older subjects are at a disadvantage compared with their younger counterparts because it takes them longer to reach a set sensitivity level because of an absolute scotopic sensitivity loss. Because we know nothing of the visual health of these adults, it is possible that pathology played a role in this large final dark-adapted sensitivity depression of about 2.0 log units

In a brief report, Luria (1960) reported final dark-adapted sensitivities for a small sample of 13 individuals (20 to 73 years old). Five of the subjects were over age 50, but only 2 were over age 60 years old. Luria was interested in the variability of each subject's thresholds. This work is significant as it was the first study to attempt to address age-related individual differences in the measurement of scotopic sensitivity within the same subject. However, the small sample of restricted age range hampers its value. Luria used a very large test field of 40° by 100° of visual angle. The subjects were dark-adapted for 30 min before testing. A method of constant stimuli was employed to determine thresholds. No correction was made for variation of pupil size or ocular media. No characterization of the visual health of the subjects was reported. Luria found that subjects over 50 years old exhibited a decline in light sensitivity compared with the subjects younger than 36 years old. Subjects who were age 50 and over had a sensitivity of about 0.36 log μμL lower than subjects under age 30. This compares well with Steven's (1946) 0.39 log unit loss for similar age ranges. Luria did not find increased

variability in the threshold measurements of older adults. It should be noted that 8 of Luria's 13 subjects were experienced psychophysical subjects, unlike Steven's subjects.

A breakthrough paper by Gunkel and Gouras (1963) examined the effect of age-related increases in lens senescence on final dark-adapted sensitivity. Gunkel and Gouras sought to identify a stimulus wavelength that demonstrated age-related changes in retinal function rather than lens density, previously ignored in the literature. In other words, is there a stimulus wavelength that would eliminate the effects of lens density and reveal neural differences as a function of age? As we have seen, violet light is very susceptible to the effects of lens density. Gunkel and Gouras studied 3 groups of subjects. One group consisted of 27 subjects, age 16 to 86 years old. A second group consisted of 18 subjects with aphakic eyes. The third group was 2 albino subjects. The subjects were tested with natural pupils. The effect of pupil size was examined by retesting a subset of the subjects with dilated eyes.

Thresholds for six different wavelengths of light were measured with a modified Goldmann-Weekers adaptometer (Gunkel & Gouras, 1963). Each subject dark-adapted from normal room lighting for at least 20 min until white light thresholds plateaued. The target subtended 10° of visual angle and was located below a dim red fixation light. Sensitivity data was reported for three wavelengths (white, red, and violet, for which the wavelength characteristics were not reported).

A progressive decrease of scotopic sensitivity with age was reported for all wavelengths. The severity of the sensitivity decline was greater as the wavelength became shorter. The sensitivity loss for violet light in the normal group was ~ 0.011 log

units per year. However, for the aphakic subjects, decline was lower (~ 0.004 log units per year). For the violet light, the aphakic subjects were more sensitive than the normal subjects for all ages. This result reflects the absence of absorption by the lens. Elderly subjects over age 80 exhibited a scotopic sensitivity loss of 1.0 log unit to violet light compared with aphakic subjects. For violet light, there was an age-related decline in sensitivity of about 2.0 log units between the oldest group and the youngest group. That sensitivity loss shrank to about 0.5 log units for red light. Again, using white light there was about 0.5 log unit sensitivity loss. Mydriatic subjects did not have significantly greater sensitivity compared with their undilated test. This result indicates that, for this sample, adequate pupil dilation was achieved during dark adaptation.

Gunkel and Gouras (1963) concluded that for violet light, most of the scotopic sensitivity loss is due to lens density because of the greater sensitivity loss as a function of age for the violet stimulus compared with the red or white stimuli. They further concluded that the effect of lens density can be minimized by using a long wavelength or white light stimulus. Sensitivity loss that was found for long wavelength or white light was attributed to pupillary light loss or neural changes, between which they could not distinguish. Gunkel and Gouras proposed examining the ratio of the subject's violet to red thresholds as an indication of senescence. One drawback to using red light to minimize the influence of lens senescence is the relative insensitivity of the rods to long wavelength light.

An attempt to control for lens density was made by Pulos (1989) while studying the rod sensitivity loss that occurs during aging. This work is significant as it was the

first study to control for both lens density and pupil size. However, the age range of the subjects limits the usefulness of the results. Pulos examined subjects under 61 years of age to avoid having to distinguish between pathology and normal aging. Pulos tested retinal eccentricities designed to detect age-related rod loss.

Pulos (1989) studied 23 subjects from 19 to 61 years old. The subjects were divided into two age groups. The young group was age 19 to 27 years old. The older group was age 50 to 61 years old. An ophthalmologic exam was performed up to a year before the study. The subjects' best corrected acuity was 20/20 or better. Post-hoc corrections for pupil size and lens density were applied to the subjects' thresholds.

After 30 min of dark adaptation, light sensitivity was measured with a Goldmann-Weekers dark adaptometer. Three stimulus wavelengths were used (460 nm, 490 nm, and 580 nm). For each wavelength, thresholds were measured at 6 retinal eccentricities (2.5°, 5°, 10°, 15°, 20°, and 30°) across the horizontal meridian in the temporal retina. The subjects were tested with natural pupils.

For the 460-nm and the 490-nm wavelengths, the young subjects were more light sensitive than the older group of subjects (Pulos, 1989). The 2 groups were equally sensitive to the 580-nm stimulus. Lenticular and macular pigment densities were estimated for each subject. Scotopic pupil size was estimated for each individual. After the thresholds were corrected for these pre-retinal factors, no age-related loss was found for any of the wavelengths. No age-related sensitivity loss was detected. Pulos' subjects may not have been old enough to find a psychophysical correlate of aging-related rod loss. Significant age-related rod loss is found to occur after age 65 years old (Curcio, Millican,

Allen, & Kalina, 1993). A complete characterization of the visual health of the subjects is a better solution than not studying adults aged 60 and up.

Coile and Baker (1992) examined the effect of age on dark adaptation of the cone-mediated visual system. They tested 58 subjects from 10 to 78 years old. All of the subjects were free of retinal pathology as determined by an eye health examination administrated in the year prior to testing. Photopigment density was measured with a retinodensitometer. The densitometer used a 580-nm visible light and a near infrared light (no wavelength specified). The subject's photopigment density was measured with both wavelengths of light. The measurement obtained from visible light is influenced by photopigment bleaching, and the near infrared light is not. Thus, the infrared measurement was a baseline measurement of the subject's photopigment density. The log ratio of the two measurements was used to track photopigment density changes. Using a method of adjustment for the visible light, absolute thresholds were determined on the densitometer. This allowed the same system to measure dark adaptation and photopigment density. An artificial pupil was used to minimize the effect of pupil size. A centrally located stimulus of 1.4° of visual angle was used as the test spot and the fixation target. The subject dark-adapted for 15 min before baseline measurements of photopigment density and threshold were made for a duration of 1 min. The subject was bleached for 1 min by a central field that subtended 5° of visual angle and a brightness of 5.8 log Td white light. Measurements of photopigment density and absolute threshold were made for the next 13 min of dark adaptation. The effect of lens density was corrected with the method reported by Said and Weale (1959).

Coile and Baker (1992) reported that cone sensitivity and photopigment regeneration decreased with age. Sensitivity loss was 0.18 log units/decade, and photopigment regeneration slowing was 0.01 log units/decade. These data suggest that a much greater change in sensitivity occurs as one ages compared with photopigment regeneration. Coile and Baker concluded that the parallel increase in time constants for dark adaptation and pigment regeneration showed that pigment regeneration played a role in the decreased dark adaptational ability. They reported that an additional 0.21 min/decade was required for both the absolute thresholds and photopigment densities to reach baseline levels. They concluded that a portion of the age-related cone-mediated scotopic sensitivity loss is a result of a change in rate of dark adaptation for cones.

Sturr et al. (1997) investigated the age-related scotopic sensitivity loss of older adults while controlling for pupil size and lens density. Sturr et al. recognized that Pulos (1989) did not test subjects of sufficient age to find age-related scotopic sensitivity loss. Of interest is the selection of wavelengths (406 nm and 560 nm) used by Sturr et al. They proposed comparing the threshold obtained with the 406-nm filter to the threshold of the 560-nm filter to quantify the effects of lens density. The 406-nm light is absorbed more than the 560-nm, light for which absorption is insignificant. The threshold was corrected for pupil size by the subtraction of 0.05 log units/decade as interpreted from Birren, Casperson, and Botwinick (1950) and Loewenfeld (1979). Sturr et al. (1997) was the first paper in this field to address the effect of response bias in this literature. To control for response bias, a criterion-free psychophysical method was employed. In

addition, all observers were tested on a second day to assess reliability of the measurements.

The sample (Sturr et al., 1997) consisted of 26 young subjects (20 to 30 years old) and 14 older subjects (62 to 84 years old). The older subjects were subjected to a full eye exam. All of the subjects had a best corrected acuity of 0.67 (20/30). Assessment of the fundus and lens allowed exclusion of subjects with cataracts or obvious retinal disease. As mentioned earlier, the publishing of the results from the eye exam is important to allow for comparisons across studies, considering the phrase "good eye health" is nebulous. Sturr et al. used a custom-built perimeter. The stimulus was a circular test spot that subtended 1° of visual angle and was located 10° from a dim red LED fixation light on the horizontal meridian in the temporal visual field. The subjects were tested with natural pupils and with their best ocular correction for distance. The testing began after dark adaptation of at least 30 min. A preliminary threshold was measured by the method of adjustment for each wavelength. Thresholds were then determined by a temporal two-interval forced choice staircase method with auditory feedback. To eliminate a practice effect, the subject practiced the forced choice method for about 5 min on suprathreshold stimuli. Sturr et al. reported that thresholds were higher for the older subjects for both the 406-nm and 560-nm wavelength. For both age groups, the thresholds on the 406-nm filter were higher than the 560-nm filter. The age-related differences in thresholds were less for the 560-nm filter than the 406-nm filter, but the differences were significant in both cases. After correction for lens density and pupil size, the older adults were 0.39 log units less sensitive than the older subjects. This

sensitivity loss was attributed to neural factors. Sturr et al. concluded that the sensitivity loss they reported could be the functional correlate of the age-related rod and ganglion cell loss found in the human retina. However, a stronger argument could be made for this connection if they tested various eccentricities in which rod loss is known to be prevalent.

Jackson, Owsley, Cordle and Finley (in press) compared the scotopic sensitivity of young and older adults in good eye health after individualized correction for age-related changes in lens density and control of pupil diameter. Unlike earlier studies on this topic, fundus photography and a grading scale were used to characterize macular health in the older sample. Twenty-four young adults (M age = 24 years) and 25 older adults (M age = 70) underwent scotopic sensitivity testing after 30 min of dark adaptation. Light sensitivity for a 450-nm target was measured at 4°, 7°, 32°, and 38° both nasally and temporally along the horizontal meridian. Lens density was estimated using Sample et al.'s (1988) method, which is described later in detail. Briefly, a perimetry-based estimate of lens density is obtained by two-color perimetry. A longer (560 nm) wavelength and shorter (410 nm) wavelength light are used for which rhodopsin is equally sensitive. The difference in threshold between these two wavelengths is attributable to lens density. After calculating an estimate of the contribution of lens density on the target wavelength, the estimated lens opacity is subtracted from the threshold.

Results (Jackson et al., in press) indicated that older adults exhibited an average 0.5 log unit decrease in sensitivity even with lens density taken into account, which did not vary with target eccentricity or nasal/temporal hemifield. This finding suggests that the scotopic sensitivity impairment exhibited by the older adults may represent a

biological aging process. Although 60% of older subjects exhibited fundoscopic signs of early age-related maculopathy, even those free from these signs demonstrated a one-half log unit sensitivity loss, suggesting that this impairment may represent a biological aging process. We found no psychophysical evidence that scotopic sensitivity loss in older adults with relatively good retinal health is accentuated in the peri-macula, even though anatomical studies on donor retinas from older adults have indicated that this area has heightened rod loss.

The macula grading scale is described in detail later, and the grading criteria is listed in Table 1. Briefly, early age-related maculopathy (ARM) was defined as the presence of 1 or more soft drusen ≥ 63 μm in diameter, the presence of focal hyperpigmentation, or both. This criterion for early ARM is consistent with previous macular grading scales used in epidemologic studies of ARM (Bird et al., 1995; Klein, Klein, & Linton, 1992; Mitchell, Smith, Attebo, & Wang, 1995; Vingerling et al., 1995). Fully 60% of older subjects exhibited the fundoscopic signs of early ARM. Older adults free from signs of ARM exhibited about a 0.5 log unit sensitivity loss. In the advanced stages of ARM, both the rate and overall level of dark adaptation are impaired (Brown et al., 1986). The grading scale we used to define normality may be too strict, as suggested by Curcio, Medeiros, & Millican (in press). Curcio et al. pointed out that using a drusen size definition of ≥ 63 μm causes many eyes to be graded as having early ARM without the presence of detectable photoreceptor degeneration. Another distinct possibility is that the measurement of scotopic sensitivity may not be sensitive enough to distinguish between the earliest stages of ARM. In summary, we found no psychophysical evidence

that scotopic sensitivity loss in older adults with relatively good retinal health is accentuated in the peri-macula, even though anatomical studies on donor retinas from older adults have indicated that this area has heightened rod loss.

Table 1
Description of the Macula Grading System

Stage[1]	Description	Subjects[2]
0	≤ 5 small (≤ 63 μm) drusen	31
1	≥ 5 small (≤ 63 μm) drusen	14
2	≥ 1 large (> 63 μm) drusen and/or focal hyperpigmentation	21
3	drusen and choroidal neovascularzation	0
4	drusen and geographical atrophy	0
5	drusen and choroidal neovascularization and geographical atrophy	0

[1] Stage 0 and 1 were considered normal. Stage 2 and higher were classified as having ARM.
[2] Number of older subjects in the present sample classified in each grade.

In conclusion, old adults exhibit a scotopic sensitivity loss that is, in part, the result of neural mechanisms. The magnitude of the scotopic sensitivity loss appears to be about 0.4 to 0.5 log units (Jackson et al., in press; Sturr et al., 1997). Photoreceptor drop-out does not appear to be the mechanism underlying the scotopic sensitivity loss (Jackson et al., in press). Although there is evidence that the rate of dark adaptation decreases with age for cones (Coile & Baker, 1992) and rods (Holopigian et al., 1997), the two studies (Birren and Shock, 1950; McFarland et al., 1960) that examined a large

number of adults found no decrease in the rate of dark adaptation with age. The reviewed literature suffers from methodological flaws and crude estimates of dark adaptation kinetics. Thus, it an open question whether the rate of rod-mediated dark adaptation changes with age.

Mechanisms of Dark Adaptation

Recent advances in research on the phototransduction system are providing possible biological correlates to the psychophysical models of dark adaptation. The site of adaptation has been attributed both to the photoreceptor itself and to an adaptation pool composed of all of the receptors converging on a single ganglion cell (Rushton, 1965; Rushton, Campbell, Hagins, & Brindley, 1955; Rushton & Powell, 1972). Much of dark adaptation can be accounted for the phototransduction pathway (Lamb, 1980). The spatial effects of bleaching suggest that a neural postreceptoral response would be necessary to explain the observed light sensitivity (Rushton, 1965).

The photochemical theory attractively bundles the site of dark adaptation into the photoreceptor itself. Hecht (1921) was an ardent proponent of the photochemical theory. This theory proposes that the process of dark adaptation is controlled by the presence of rhodopsin in the rods. When rhodopsin is struck by light, rhodopsin activates the phototransduction pathway and becomes insensitive to light. The amount of bleached rhodopsin is directly proportional to the psychophysical threshold (Hecht, 1921). However, it was not until 35 years later that the photochemical theory could be directly tested.

With the development of the retinodensitometer by Campbell and Rushton (1955), it was possible to measure the regeneration rate of rhodopsin and infer the visual threshold. This allowed the first direct testing of the photochemical theory. In an experiment performed on a rod monochromat, Rushton (1965) found that the log visual threshold was directly proportional to the fraction of rhodopsin present. Dowling (1960) used electroretinogram recordings to measure the visual thresholds of rats during dark adaptation and objectively measured the rhodopsin concentration of the rat eye at various time intervals during dark adaptation. He found that the log of the visual threshold was directly proportional to the amount of bleached rhodopsin. From Rushton's and Dowling's work, the Dowling-Rushton equation was derived: log threshold elevation = a constant * concentration of bleached photopigment. The constant in humans was found to be 20 and was later revised to 12 for the rods and 3 for the cones (Rushton, 1965; Rushton & Powell, 1972). The model best fits the late stages of recovery from moderate bleaches. The model grossly underestimates the effect of small bleaches. For example, the model would predict that a 2% bleach would produce 0.4 log unit threshold elevation, when experimentally the threshold elevation is about 3 log units. The model also poorly fits empirical data collected for large bleaches. Although the photochemical theory embodied by the Dowling-Rushton equation was discredited, the search continued for a mechanism of dark adaptation that was intrinsic to the photoreceptor.

Another explanation for the mechanism of dark adaptation is the equivalent background hypothesis (Crawford, 1937). This theory proposes that the "dark light" or "equivalent light" produced by bleaching has the same effect as a stabilized field of real

light that decays with time. The bleaching light produces a stabilized afterimage for which the target stimulus must be brighter than if the subject is to detect the stimulus. Typically, dark adaptation and increment threshold curves with continuous backgrounds are measured using identical stimulus parameters. Equivalent background functions are produced by selecting a continuous background intensity that produces a threshold that is also found on the dark adaptation curve. If the dark adaptation curve and the equivalent background curves match, this is considered proof of the theory (Geisler, 1980). This explanation serves to unify light and dark adaptation processes such that dark adaptation is a special case of light adaptation. This theory estimates the effect of small and large bleaches better than the Dowling-Rushton equation. Initially, the equivalent background theory was criticized as unphysiologic (Rushton, 1965). The theory dictated that the visual system would have to behave in response to a decaying real background light in the absence of such a light.

Lamb (1981) looked to the phototransduction pathway to provide the physiological basis of equivalent light as necessitated by the equivalent background theory. Lamb (1980) recorded the current of a rod from a toad after exposure to a light that produced 0.7% bleach of rhodopsin. The results demonstrated that the dark current was eliminated in light. After light exposure is terminated, the current slowly increased with increased noise, consistent with the findings of Baylor, Mathews, & Yau (1980). The noise is described as photon-like events. By varying the background light, the current resembled the current found in response to transient bleach. The conclusion from these experiments was that the resulting behavior of the rod recovery from bleach is

equivalent to the recovery expected from a continuous background field of decreasing luminance. Lamb (1981) attributed the response of the rods to a model of phototransduction reliant on reverse reactions from photoproducts of rhodopsin. Experiments using large bleaches show that the initial portion of dark light recovery is free of photon-like events and is attributed to a second messenger system (Leibrok, Reuter, & Lamb, 1994).

Recently, Lamb, Pugh, Cideciyan, & Jacobson (1997) proposed the biological substrates of Lamb's (1981) original hypotheses. They proposed that rod recovery consists of 3 components, consisting of the decay of 3 photoproducts. The first component of recovery is only apparent for very small bleaches. The second component of recovery follows first order kinetics for bleaches smaller than 10%. For larger bleaches, the second component is rate limited. Lamb et al. proposed that the second component of recovery is dependent on the diffusion of 11-*cis* retinal from the retinal pigment epithelium to the rod outer segment. They believed the translocation of 11-*cis* retinal and the binding coefficient of retinal binding protein is concentration dependent. Thus, an alteration in the 11-*cis* retinal available in the retinal pigment epithelium and the diffusion constant of the retinal binding protein should alter sensitivity recovery during the second component of dark adaptation. In fact, the model accurately predicts the recovery of dark adaptation in subjects with vitamin A deficiency (Cideciyan et al., 1997). The third component of recovery is thought to be rate-limited by the recycling of retinoid. The model accurately predicts the recovery from a large range of bleach intensities (2% to 99%).

Two possible mechanisms for age-related changes in dark adaptation are age-related changes in the photoreceptor mosaic and age-related alterations in photo-transduction. Age-related photoreceptor loss is a potential mechanism for age-related changes in dark adaptation and scotopic sensitivity. Curcio et al. (1993) examined 27 whole, mounted, donor retinas (27 to 90 years old). Cell counts were made of rod and cone photoreceptors for the central 43° of vision. It was found that qualitatively the appearance of the aged photoreceptor mosaic was similar to that of the younger retinas. The density of cones and the total number of cones were not found to decrease significantly with age. However, rod counts within 4 mm of the foveal center revealed a significant decline in the total number of rods as a function of age. The greatest amount of age-related rod loss occurred 0.5 to 3.0 mm from the foveal center. Curcio et al. (1993) predicted that a retina of age 90 would have rod loss in the central 28.5° of vision of about 30% compared with those at age 34. The rod loss was found to start about age 45 and reach its greatest extent in the ninth decade of life. No appreciable rod loss was found in the far periphery (13 mm temporal) of the retina.

Age-related alterations in phototransduction could be caused by a localized scarcity of factors, such as 11-*cis* retinal necessary for rhodopsin regeneration. Bruch's membrane allows the diffusion of vitamin A and other nutrients necessary for retinal health to the retinal pigment epithelium. Anatomical studies indicate that Bruch's membrane thickens and changes in composition with age, and, possibly, an increasing concentration of lipid deposits develops with age (Moore, Hussain, & Marshall, 1995). These changes are thought to lead to a compromised exchange efficiency across the

membrane (Grindle & Marshall, 1978). This decreases hydraulic conductivity and may impede the transport of water soluble molecules such as vitamin A across the membrane. Of course, the lack of vitamin A available to the retinal pool inhibits the regeneration of rhodopsin. The impairment of rhodopsin regeneration leads to night blindness. Subjects with vitamin A deficiency exhibit a delayed rod-cone break, and the rate of rod recovery is slowed (Cideciyan et al., 1997; Hecht & Mandelbaum, 1939). Disruption of normal Bruch's membrane functioning has been implicated as the part of the mechanism of Sorsby's fundus dystrophy and age-related macular degeneration (Chen, Fitzke, Pauleikhoff, & Bird, 1992; Grindle & Marshall, 1978; Jacobson et al., 1995; Pauleikhoff, Chen, Chisholm, & Bird, 1990; Steinmetz, Haimovici, Jubb, Fitzke, & Bird, 1993).

Dark Adaptation and Disease

Although the focus of this dissertation is normal aging, given the high prevalence of disease in older adults it is useful to examine the relationship between retinal diseases and dark adaptation. In addition, the slowing of dark adaptation may be caused by a combination of both aging and disease. Many researchers are interested in the application of dark adaptometry as a research tool investigating Sorsby's fundus dystrophy and ARM (Brown et al., 1986; Jacobson et al., 1995). The research on these diseases provides a wealth of information that allows one to ask whether the aging-related decline in dark adaptation is a symptom of subclinical pathology or is caused by an aging-specific mechanism.

Sorsby's fundus dystrophy. Sorsby's fundus dystrophy is a rare autosomal dominant retinal degeneration that has an early age of onset. Although Sorsby's fundus dystrophy is rare, it is of interest as it is thought to be have a similar mechanism as age-related macular degeneration (AMD). An extreme thickening of Bruch's membrane is seen in this disease. Early symptoms include complaints of night blindness by the patient. As the disease progresses, loss of central vision and, later, peripheral vision occurs by subretinal neovascularization and hemorrhage (Capon, Polkinghorne, Fitzke, & Bird, 1988). One hypothesis for the mechanism of the vision loss is a decreased exchange efficiency of Bruch's membrane that impedes the diffusion of vitamin A across Bruch's membrane. The early effect of slowed diffusion across Bruch's membrane is thought to be a slowed rate of photopigment regeneration because of a localized vitamin A deficiency in the retina. Attempting to determine the effect of vitamin A therapy on this disease, Jacobson et al. (1995) studied both scotopic sensitivity and dark adaptation in 4 subjects. Dark adaptation was performed on a modified HFA. The target was a 500-nm circular test spot that subtended 1.7° of visual angle. After exposure to a greater than 95% bleach, 1 subject with Sorsby's fundus dystrophy exhibited a cone/rod break 35 min into dark adaptation compared with 12 min for a control subject. The same subject exhibited a scotopic sensitivity loss of about 1.0 log unit at most points tested in the visual field and had a scotoma of 4.0 log units in the left hemifield along the horizontal meridian. Jacobson found that afflicted patients have a lower scotopic sensitivity and a slower rate of dark adaptation and that the severity of these losses became greater with the progression of disease. Vitamin A was administered at 10 times the recommended daily

allowance for 1 month. Supplementation of vitamin A restored some to most of the afflicted subjects' night vision depending on the stage of Sorsby's fundus dystrophy. Night blindness disappeared in as little as a week for those subjects in the early stages of the disease. Supplementation of 5,000 I.U., the dosage commonly found in multivitamins, was not sufficient to maintain the gains in sensitivity found with the higher dosage. The vitamin A treatment is thought to act by mass action to elevate the vitamin A level available to the retinal pool. Even if a systemic vitamin A deficiency is not present, the retinal pool of vitamin A can be deficient because of transport blockage across Bruch's membrane. If the normal age-related thickening and composition changes found in Bruch's membrane impede vitamin A from reaching the retina, age-related scotopic sensitivity loss might be the result.

Age-related macular degeneration. In the western world, age-related macular degeneration is the leading cause of blindness in individuals over 50 years old (Bressler, Bressler, & Fine, 1988). An accumulation of debris in diffuse or discrete deposits is found in Bruch's membrane. Drusen are discrete deposits that are correlated with the risk of age-related macular degeneration and the severity of visual loss. The existence of diffuse deposits is thought to be evident by a choroidal perfusion abnormality as detected by fluorescein angiography. A diffuse deposit of debris across Bruch's membrane may explain sensitivity loss in areas of the AMD retina in which drusen are not evident.

Sunness, Massof, Johnson, Finkelstein, and Fine (1985) examined the effect of AMD on scotopic sensitivity as a function of eccentricity. They wanted to know if the

progression of AMD found in the central visual field was mirrored or preceded by changes in the peripheral portion (>15°) of the visual field. The sample consisted of 21 subjects diagnosed with AMD (57 to 80 years old) and 23 normal subjects (19 to 50 years old). All of the AMD subjects had an acuity of 20/60 or better in at least one eye, and the eye with the better acuity was tested. The eye was patched for 1 hr. Thresholds were measured on a Tübinger perimeter. Two wavelengths (656 nm and 500 nm) were employed to examine cone and rod sensitivity. The target subtended 2° of visual angle. The test pattern consisted of 19 locations across the horizontal meridian of the visual field. For the red (656 nm) stimulus, the AMD subjects exhibited a decreased scotopic sensitivity in the central 10° of the visual field. The blue-green (500 nm) stimulus produced a greater scotoma in the central visual field. Sunness et al. concluded that for the blue-green filter, the small sensitivity difference found in the periphery was probably attributable to lens density. A similar rod scotoma was found in SFD (Jacobson et al., 1995).

Brown et al. (1986) examined the dark adaptation function as well as scotopic sensitivity in order to gain insight into the mechanism of AMD. The sample consisted of 4 subjects (67 to 74 years old) with AMD and 5 normal subjects (58 to 74 years old). The subjects had relatively good best corrected acuity ranging from 20/25 to 20/40. No correction for pupil size or lens density was employed. Thresholds were measured with a custom-built perimeter. Two wavelengths (635 nm and 565 nm) that subtended 2° of visual angle were used to isolate the cone and rod response, respectively. After dark adaptation of 20 min, scotopic sensitivity was measured at three eccentricities (0°, 5°,

25°) on the horizontal meridian in the nasal visual field. The subject was rested before dark adaptometry began. Dark adaptometry used both the 635-nm 565-nm test targets and was located at 15° of eccentricity in the nasal visual field. After 6 min of exposure to a 1160 cd/m^2 bleaching light, thresholds were measured for 20 min. The results indicated that AMD subjects exhibited a decreased cone and rod scotopic sensitivity as well as an increased cone/rod transition time compared with normal subjects. Three of the AMD subjects exhibited cone plateau thresholds about 0.8 of a log unit higher than the normal subjects. The final rod thresholds were elevated about 1.0 log unit higher than the normal subjects. Scotopic sensitivity was significantly different between the two groups out to 25° of eccentricity. The greatest scotopic sensitivity loss was found in the central 15°. Brown et al. concluded that the observed alteration of the kinetics of dark adaptation for rods resulted from altered retinal photochemistry.

The effect of diffuse deposits in Bruch's membrane on dark adaptation has been examined recently. Analyzing fluorescein angiograms of 100 subjects diagnosed with AMD, Pauleikhoff et al. (1990) found prolonged choroidal filling (rate that dye becomes visible) in 26 subjects. Prolonged choroidal filling is thought to be evidence of diffuse drusen. Chen et al. (1992) examined the relationship between prolonged choroidal filling and visual sensitivity. Eight eyes (55 to 78 years old) with prolonged choroidal filling and 6 control eyes (54 to 72 years old) with a similar number of drusen were tested. The subjects were a subset of those tested in the Pauleikhoff et al. (1990) study. The visual acuity of the abnormal choroidal filling was 6/5 to 6/12 and in the normal group was 6/5 to 6/9. The subjects were dark adapted so that pupil diameter was 6 to 7 mm. After dark

adaptation of 45 min, scotopic sensitivity was measured on a modified HFA. The test pattern was a modified 30-2 that tests the central 30° of the visual field. The target was a 506-nm circular spot that subtended 1.7° of visual angle. In addition, subjects were tested with a procedure called fine matrix mapping. Briefly, the subjects' sensitivity was tested at 100 locations in the central 20° of vision by presenting blue targets that subtended 10 min of arc on a television screen. Scotopic sensitivity loss was calculated for each point based on normative data collected on subjects 30 to 42 years old. Visual sensitivities were superimposed over their corresponding retinal locations on a print of the fluorescein angiogram. Results from the HFA showed a discrete area of sensitivity loss greater than 1 log unit in 6 of 8 subjects in the abnormal choroidal perfusion group that was not evident in the control group. From the fine matrix mapping experiment, 7 of 8 subjects with the abnormal choroidal perfusion exhibited sensitivity loss greater than 1 log unit in discrete areas that corresponded to the area of slow choroidal filling. Chen et al. concluded that visual decline in AMD is also caused by diffuse changes in the retina beyond those caused by drusen. This study supports the conclusion that diffusion is impeded at the level of Bruch's membrane. The blockage of large molecules such as vitamin A diffusing through Bruch's membrane may account for some of the sensitivity loss found in the psychophysical literature.

Some patients in the early stages of age-related macular degeneration have good acuity but have poor nighttime vision and a central scotoma noticeable in the dark. Steinmetz et al. (1993) measured dark adaptation in subjects with such symptoms. Complete ophthalmologic exams were performed on 12 subjects (54 to 86 years old) to

rule out other systemic diseases such as liver cirrhosis that affect dark adaptation. Half of the subjects exhibited abnormal choroidal perfusion. The subjects were dilated to a pupil size of 6 mm or greater to avoid the effect of pupil size. After dark adapting for 45 min, the subjects' scotopic sensitivity was measured with a modified HFA. A 30-2 test pattern which tests sensitivity in the central 30° of the visual field was used. The target was a 450-nm circular spot that subtended 1.7° of visual angle. Five of the subjects had their sensitivity measured to a target produced by a 608-nm cutoff filter. The 608-nm target was two different sizes (0.8° and 1.7° visual angle). Dark adaptometry was performed in two locations. One location was chosen where the scotopic sensitivity was considered normal, and another location was selected in which the sensitivity was abnormal. Abnormal sensitivity was defined as a sensitivity loss of 1 log unit or more compared with normal subjects. The subjects were bleached for 2 min to produce a greater than 95% bleach. Measurement of dark adaptation was terminated when sensitivity returned to within 0.5 of a log unit of prebleach sensitivity. Dark adaptation was considered prolonged if termination occurred outside the range of normal values for age-matched controls. Termination of dark adaptation was prolonged in 10 of the subjects, and in 8 subjects, dark adaptation did not terminate 60 min after bleach. In a majority of the sample, both cone and rod regeneration constants were abnormal. Four of the subjects exhibited both abnormal final scotopic sensitivity and dark adaptation kinetics. Interestingly, 6 of the subjects had normal scotopic sensitivity and abnormal dark adaptation kinetics.

Curcio, Medeiros, and Millican (1996) examined whether age-related rod loss was actually subclinical age-related macular degeneration by quantifying cones and rods in 3 donor eyes with nonexudative AMD compared with age-matched controls. Cell counts of cones and rods were made in donor eyes in the mid to late stage of AMD. Foveal sparing of cones was found. In all 3 cases, photoreceptor loss was found in an annulus from 0.5 mm to 3.0 mm around of fovea. In this area, the photoreceptor density was 60% to 70% of age-matched controls. Eccentricities outside of 3.0 mm from the fovea were virtually normal. Two of the three eyes exhibited more rod loss than cone loss in this annulus. This finding may provide an anatomical correlate for the central rod scotoma found in AMD. However, 1 subject exhibited more cone loss than rod loss. The selective nature and location of rod loss in the present study correspond to the previous findings in normal eyes (Curcio et al., 1993).

Jackson et al. (1997) examined whether a psychophysical correlate of the selective vulnerability of rods reported by Curcio et al. (1996) could be demonstrated. This study compared the photopic versus scotopic sensitivity of 53 ARM patients with 11 older adults in good retinal health. Individual lens density estimates were used to correct thresholds which were measured with dilated pupils. To characterize the macular health of patients, a macula grading scale was used (Jackson et al., in press). The grading scale was used to group the subjects by macular health into the normal group and ARM group. The visual fields were performed on a modified HFA (Humphrey, Inc.): (Chen et al., 1992; Jacobson et al., 1986). The modifications of the HFA are described in the methods of this dissertation. For photopic testing, the wavelength of the target was 600 nm, and a

500-nm target was used for scotopic testing (600-nm Ealing # 35-3821, FWHM 10.1, Peak 50%; 500-nm Ealing # 35-3508, FWHM 7.4, Peak 50%). The target was a Goldmann size V (1.7° visual angle). The test pattern consisted of 52 loci and was designed to provide good coverage of the macular area in the central 36° of the visual field. The subject adjusted to the dark for 40 min prior to the scotopic visual field testing. Averaging the sensitivity across all 52 loci, the mean photopic sensitivity was 0.23 log units less for the ARM patients compared with the normal patients. Similarly for the scotopic field, the ARM patients exhibited a mean sensitivity loss of about 0.85 log units. The scotopic sensitivity loss was greater in the central 20° of the visual field. Difficulty with nighttime driving was assessed with the Activities of Daily Vision Scale (ADVS) developed by Mangione et al. (1992). Analysis of the ADVS results indicated that the total ADVS score was 23.76 points lower for the ARM patients compared with the normal patients. ARM patients expressed more difficulty with far vision tasks and glare but not near vision tasks and daytime driving. Of interest, ARM patients expressed more difficulty with nighttime driving compared with those in good eye health, and their reported difficulty varied proportionally to their scotopic sensitivity loss.

In an effort to quantify the extent of peripheral field deficits in ARM patients, Holopigian et al. (1997) measured the rate and overall level of dark adaptation in 10 ARM patients (range 66-84 years) and 23 normal patients (range 23-81 years). The rate of dark adaptation was quantified as the rod-cone break. Dark adaptation was measured at 2 retinal eccentricities, 7° and 15° in the temporal retina. The stimulus was a 1.2° circular test spot of white light. The threshold sampling rate was 1 threshold every 30 to 60 sec.

The duration of dark adaptometry was about 35 to 40 min. In the normal patients, the rod-cone break increased at a rate of 0.04 min/year. Subjects in their 80s exhibited a delay in rod-cone break of about 2.4 min compared with subjects in their 20s. A normal range of rod-cone breaks was established by computing the 95% confidence limits of the control group's rod-cone breaks. Four of 10 ARM subjects' rod-cone breaks were worse than normal. Normal patients in their 80s exhibited a final dark-adapted threshold elevation of 0.6 log unit compared with normal patients in their 20s. Only 2 of the ARM patients had thresholds that were worse than the normal range of the control subjects. Holopigian et al. concluded that many of the ARM patients were indistinguishable from normal patients in dark adaptation function when aging was taken into account.

Dark Adaptation and Activities of Daily Living

Impaired scotopic sensitivity and dark adaptation may contribute to the difficulty older adults experience under conditions of dim illumination. A more serious public health problem is the possibility that poor night vision puts the elderly population at a greater risk of debilitating injuries resulting from automobile crashes or falling. Extending the ability of the elderly to maintain health and independence is essential to contain health care costs. Some problems that older adults experience with driving, falls, and reading under dim illumination are discussed below.

Elderly drivers 65 years old or older have more fatal nighttime automobile crashes than any group except those drivers under age 25 (Moritmer & Fell, 1989). There is an empirical dearth of knowledge regarding age-related decline in dark adaptation and

performance of the driving task. Some researchers have proposed that the impaired ability to dark adapt could compromise driving performance (Brody, 1954; McFarland et al., 1960; McMurdo & Gaskell, 1991).

Ball et al. (in press) examined 257 older drivers' visual and cognitive impairment and their avoidance of challenging driving situations. Visual function was characterized by measuring the subject's acuity, contrast sensitivity, and photopic visual field screening. Cognitive function was measured by the Mattis Organic Mental Status Syndrome Examination. Also, the size of the useful field of view was measured. The Driving Habits Questionnaire was used to measure driving exposure and avoidance of challenging driving situations. The subjects were asked whether they avoid nighttime driving, high traffic roads, rush-hour traffic, interstates, driving alone, left-hand turns against oncoming traffic, and driving in the rain. Results indicated that most of the subjects frequently avoided nighttime driving and rush-hour traffic. Based on the cognitive and visual function results, subjects were classified into unimpaired or impaired groups. Unimpaired and impaired subjects avoided nighttime driving with the same frequency, although the functional groups differed significantly on the other avoidance items. Ball et al. concluded that older adults increased avoidance of nighttime driving could be attributable to a safety strategy employed by older drivers. However, the night vision of the subjects was not characterized, so it remains an open question whether these subjects were visually impaired under low illumination. Each subject's eye health was rated by an ophthalmologist and grouped by primary diagnostic category into the normal, cataract, or AMD group. Compared with normal subjects, subjects with AMD reported more

difficulty with all activities, including nighttime driving. This result is consistent with the finding that AMD patients report more difficulty with nighttime driving found on ADVS (Jackson et al., 1997; Mangione, Ajani, Padan, Orav, & Seddon, 1994).

Kline et al. (1992) surveyed drivers of various ages to examine their visual problems. Almost 400 people across a wide cross section of ages were surveyed. Most of the subjects reported being in good physical and visual health. The survey was divided into three sections. The first part included questions about demographics and general visual health. The second part asked about everyday visual tasks, and the last portion examined visual difficulty with various driving tasks. The results indicated five areas of difficulty identified with age. Visual processing speed, dim illumination, dynamic vision, near vision, and visual search all were identified to be impaired with age. With increasing age, drivers noted more difficulty in reading the instrument panel. Older drivers reported that taillights of other vehicles were too dim more often than did younger drivers. Also, the old drivers expressed the desire that street lights would turn on sooner. Kline et al. demonstrated that drivers reported changes in driving habits in response to declining visual ability. Older drivers tended to avoid specific driving habits or to employ some compensatory behavior. For instance, driving at night or during rush hour is curtailed. The authors pointed out that these curtailments may be because of lifestyle changes related to age and not to decline in visual function. Also, the authors pointed out that older adults have insights into their changing vision, and those insights should be used to guide empirical research. This type of work serves to demonstrate the need to study night vision and aging, but this research would be more useful if visual function were

characterized in the same subject population as the one used to generate the self-report data.

Estimates suggest that 25% of the people over 70 years old, rising to 35% for adults over 75 years old, suffer accidental falls (Tinetti & Speechley, 1989). Moreover, one half of the people who suffer one fall experience repeat falls (Tinetti & Speechley, 1989). These incidence rates rise for the institutionalized elderly population. The severity of this experience is shown by the fact that 70% of all fall-related deaths in the United States occur in the elderly population (Commodore, 1995). Most of the negative consequences affecting the quality of life of the elderly faller are attributed to complications of the accidental fall (Speechley & Tinetti, 1991). More older adults are committed to nursing care after suffering a fall than any other accident (Alexander, Rivara, & Wolf, 1992). It is estimated that the cost of falls to persons of the United States by older adults is from 75 billion to 100 billion dollars a year in direct and indirect costs (Urton, 1991). This results in a restriction of activity and social interaction. After suffering a fall, some elderly people have their activities restricted by their family (Walker & Howland, 1991). The relationship between night vision and falling is not well established, although it has been found that a significant number of falls occur in the late afternoon and evening (Hongladarom, 1983; Walker & Howland, 1991). Nighttime falls by elderly persons occur with a greater frequency at residential care facilities than homes (Gryfe & Amies, 1977).

McMurdo and Gaskell (1991) studied fallers and nonfallers in a nursing home setting and compared their ability to dark adapt. The sample consisted of 22 female

patients whose average age was 84 years old. Fallers were operationally defined as having experienced 3 or more falls in a 2-month period. The control group had experienced no falls during the same time period. Ophthalmologic history of each patient was recorded, and visual acuity was measured. Fundoscopy and cataract screening were employed to rule out poor visual health. After bleaching with a photographic flash gun, the dark adaptation curve was run for 20 min with a threshold recorded every min. The 2 groups were equivalent in age and acuity. At 5 min of dark adaptation, there was a significant difference in sensitivity so that nonfallers performed better than fallers. There was a 0.5 log unit sensitivity difference between the 2 groups. This significant difference was also reflected in the 20th min of the dark adaptation curve because the difference in sensitivity between the 2 groups rose to 1.0 log units. Normal values were obtained for younger subjects to serve as a control group. The younger subjects were 0.2 log units worse than the nonfallers in this experiment at 5 min of dark adaptation. The younger subjects were 0.5 of a log unit better than the normal observers at 20 min of dark adaptation. The results seem to indicate that older adults who were classified nonfallers tend to do almost as well as their younger counterparts. Older adults classified as fallers by this performance measure show a deficit in their ability to dark adapt. The abnormal dark adaptation found in fallers seems not to be caused by differences in acuity or cataract formation. However, it is unknown whether this decrease in dark adaptational ability is because of a generalized decrease in light sensitivity or some component of dark adaptation itself.

McMurdo and Gaskell's (1991) study was unclear about some of the experimental conditions. No mention was made of the stimulus parameters. The intensity of the bleach or the wavelength of the test target was not quantified. One would assume that the lack of mention of the stimulus wavelength would indicate that a white light was employed. Perhaps the greatest failing of the paper is the lack of control over the variables that are frequently associated with increased risk of falling, such as gait. The significance of this study lies in the fact that the authors show a correlation between impairment of dark adaptation and functional consequences.

Usually, reading in dim illumination can be avoided and is an inconvenience. However, reading street signs under low illumination can affect the safety of the older driver and other road users. Many citations and crashes attributed to the elderly are attributed to failure to obey traffic signs. Not being able to read signs in time for an appropriate response has been suggested to result in the failure to yield or other dangerous behavior. Babbitt-Kline, Ghali, Kline, & Brown (1990) sought to determine whether icon-based or text-based street signs were more visible to older drivers. This assessment was conducted under daytime and dusk illuminations. The sample consisted of 48 subjects evenly split into 3 age groups: young (18 to 34 years old), middle aged (45 to 60 years old), and old (61 to 72 years old). All of the subjects were tested with best corrected acuity, and there was not an age-related difference in acuity. The icon and text version of four regulation signs (Divided Highway, Road Narrows, Men Working, and Hill) were used for testing. Video images of the signs were displayed on a high contrast video monitor. The apparent distance to the sign was simulated by adjusting the

magnification on the video camera that caused the sign to change size on the video monitor. The illuminance of the monitor and ambient illuminance of the room were 10 cd/m^2 for the dusk condition and 65.0 cd/m^2 for the daylight condition. The subjects binocularly viewed the monitor from a fixed headrest. The smallest sign height for which the subject could give a description of the sign was recorded. The subject was also asked to give the meaning of the sign. Icon signs were more visible than text signs so much so that the icon sign could be half the size as the equivalent text sign and still be correctly recognized. Not surprisingly, signs had to be bigger for the dusk condition than the daylight condition. The difference between icon and text sign visibility was greater at dusk than daylight. Icon signs viewed under dusk conditions were more visible than text signs viewed under daylight conditions. However, no main effects or interactions were found because of age, which is in contradiction to self-reported problems found in the literature. The explanation for the lack of age-related effects was assumed to be because of to the high level of visual function of the old group as measured by acuity (mean acuity of 1.12 min arc). Dark adaptation was not simulated in this experiment as the subject was fully adapted to the dusk illumination before testing began.

METHOD

Introduction

The goal of this project was to provide a greater understanding of the relationship between aging and dark adaptation. The kinetics of dark adaptation were examined in adults of excellent visual health. To address this specific aim, dark adaptometry was performed on 94 subjects (23-81 years old) of excellent visual health.

Several methodological improvements were made over studies reported in the previous literature. Stringent inclusion criteria for the retinal health of the subjects were used to minimize the presence of pathology in the sample. Adults age 50 and older had fundus photographs made so that the subjects' macular health could be rated by a macular grading scale. In addition, subjects were visually characterized using standard clinical tests of visual function so that comparison to previous and future studies would be facilitated. All scotopic thresholds were corrected for pupil size and lens density. Because the decline in the rate of dark adaptation during aging may be relatively small, a large bleach (98%) was used to accentuate any effects that may be undetectable with a smaller bleach because of noise. A relatively high threshold sampling rate was used to better estimate the kinetics of dark adaptation. To analyze the results of dark adaptometry, a newly developed non-linear regression technique was used to objectively and efficiently estimate the kinetics of dark adaptation. The following kinetics of the dark

data: rod-cone break, slope of the second component, slope of the third component, rod transition, and time to baseline. The parameter estimates were chosen based on developing physiological models of dark adaptation and phototransduction.

Subjects

Subjects were recruited from the Primary Care Clinic of the University of Alabama at Birmingham School of Optometry. To be included in the sample, the subject was required to have undergone an eye examination at the School of Optometry in the year prior to testing. The best-corrected visual acuity (distance) in the eye to be tested psychophysically had to be 20/25 or better, as listed in the medical record from the most recent eye exam. No subject with a diagnosis as listed in the medical record (either eye) of age-related macular maculopathy, glaucoma, diabetic retinopathy, optic neuritis, or any other eye disease that is known to compromise vision was included in the study. Also, no subject was admitted into the study with a history of any neurological condition, including Parkinson's disease, Alzheimer's disease, stroke, or other diseases that compromise vision or the subject's ability to understand and execute the protocol.

Prospective subjects who met the inclusion criteria by screening of their medical record were contacted with a letter describing the purpose and nature of the study. A follow-up phone call was made to invite the prospective subject to participate in the study. The nature and purpose of the study were fully explained before the testing session was scheduled. Before testing began, subjects signed a document of informed consent that detailed the protocol, and all testing was done in compliance with the

declaration of Helsinki and the Institutional Review Board of the University of Alabama at Birmingham (Appendix A).

Test Protocol

Subjects participated in one testing session. The protocol was carried out in the following order: visual function assessment, questionnaires, lens density estimation, baseline scotopic sensitivity measurement, dark adaptometry, and fundus photography (Figure 2). The protocol's duration was about 3 hr, including relaxation periods. In each of the visual tests, the subjects wore their best optical correction for the test distance.

Visual Function Assessment

The visual function assessment included the measurement of visual acuity, contrast sensitivity, photopic visual field sensitivity, and scotopic visual field sensitivity. Each of the visual function assessments is discussed in detail below. Subjects were excluded from the study if their best-corrected distance acuity was less than 20/25 in either eye on the day of testing. If the subject exhibited an average photopic sensitivity of less than 15 dB or an average scotopic sensitivity less than 30 dB, the subject was excluded. None of the subjects had to be excluded on the day of testing from the study. Although characterizing the visual health of the subjects required a significant amount of time, it was necessary for two reasons. The most apparent reason was to ensure as much as possible that subjects were free of ocular pathology because this study focused on normal aging. The other reason was to obtain a sample that was well characterized from a

visual function standpoint. This aided in the comparison of the resulting dark adaptation data to other studies.

Visual acuity. Subjects' letter acuity was measured with the Early Treatment Diabetic Retinopathy Study chart (ETDRS) for each eye separately (Ferris, Kassoff, Bresnick, & Bailey, 1982). This standardized chart was designed to serve as an accurate and reliable method for measuring the log minimum angle resolvable (LogMAR). The ETDRS chart has 5 letters on each line, and each line decreases geometrically in size. Each line is composed of various letters so that each line is of equal difficulty. The translucent chart was rear-illuminated by a light box that produces a mean illumination of 100 cd/m^2 on the surface of the chart. The subject viewed the chart from a distance of 4.2 m. To be included in the study, a subject had to have a best-corrected acuity of 20/25 or better in the eye to be tested.

Contrast sensitivity. Large letter contrast sensitivity was measured with the Pelli-Robson chart for each eye separately (Peli, Robson, & Wilkins, 1988). The Pelli-Robson chart measures how much contrast is needed to identify letters that decrease in contrast rather than size. Each of the chart's 8 lines consists of two groups of three letters. Each group decreases in contrast by a factor of $1/\sqrt{2}$ compared with the previous letter group. Performance on the chart was expressed as log contrast sensitivity. Pelli-Robson contrast sensitivity is related to the peak of the contrast sensitivity function for sine wave gratings and also for low spatial frequencies (Rohaly & Owsley, 1993) The chart's mean luminance was 100 cd/m^2, and each subject viewed the chart from a distance of 1.0 m.

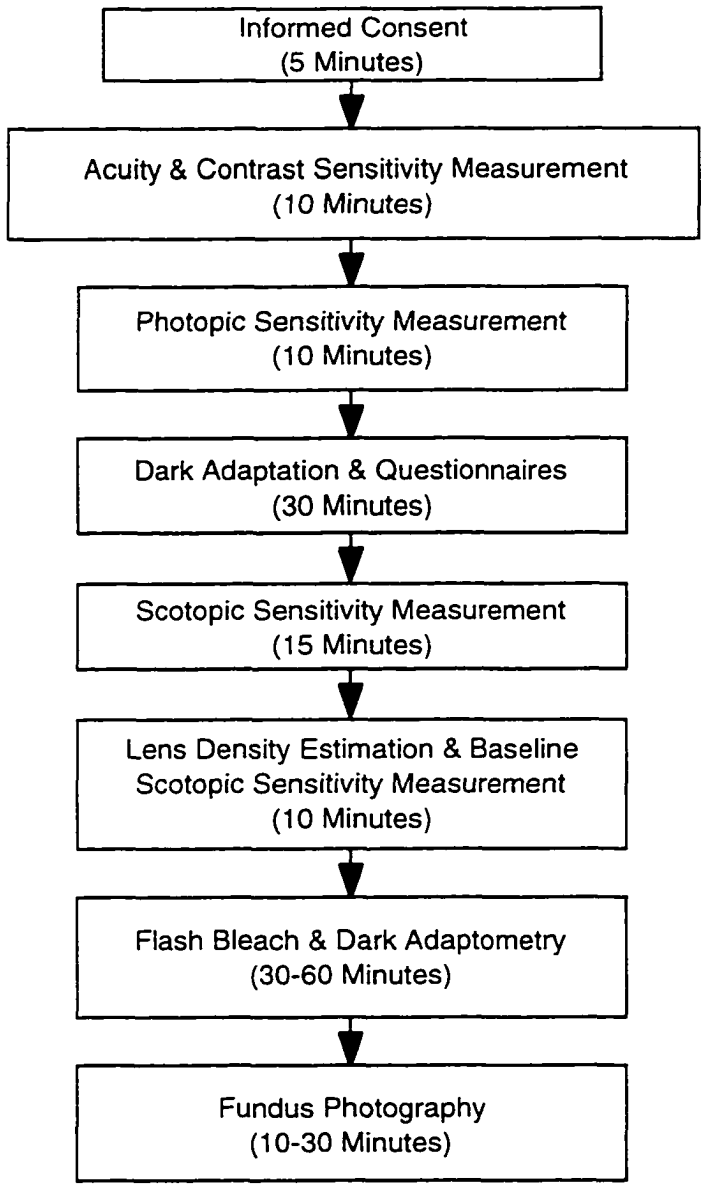

Figure 2. Protocol Flow Chart. This flow chart shows the order of the protocol and the duration of time for each segment.

Photopic Visual Field Sensitivity

Photopic sensitivity in the central 18° of the visual field was measured with a custom 28-point full-threshold test on the HFA. The HFA is a computer-automated perimeter. The subject views the stimulus projected on a Ganzfeld bowl at a distance of 30 cm from fixation. The stimulus was a 600-nm (Ealing # 35-3821, FWHM 10.1, Peak 50%), Goldmann size V (1.7° visual angle), circular test spot. The stimulus duration was 200 msec. The background had a mean luminance of 10 cd/m^2. The test pattern consists of 14 points each on the horizontal and vertical meridian, thus 28 points total. The eccentricity of the points in visual angle are -18°, -12°, -10°, -8°, -6°, -4°, and -2°, 2°, 4°, 6°, 8°, 10°, 12°, 18° (Figure 3). The HFA's full threshold strategy uses a modified 4-2 staircase threshold strategy (Cornsweet, 1970). The details of a similar threshold strategy are presented below. The subject was instructed to fixate on a red LED fixation light in the center of the Ganzfeld bowl. Fixation was monitored using the built-in fixation monitor of the HFA. Randomly, the HFA presented a light in the visual field corresponding to the location of the subject's blind spot. If the subject detected the light, a fixation error was recorded. If the number of fixation errors was greater than 10% of the number of presentations, the subject was excluded from the study. The subject responded that the stimulus was seen by pushing a button. As mentioned earlier, an average sensitivity less than 15 excluded the subject from the study.

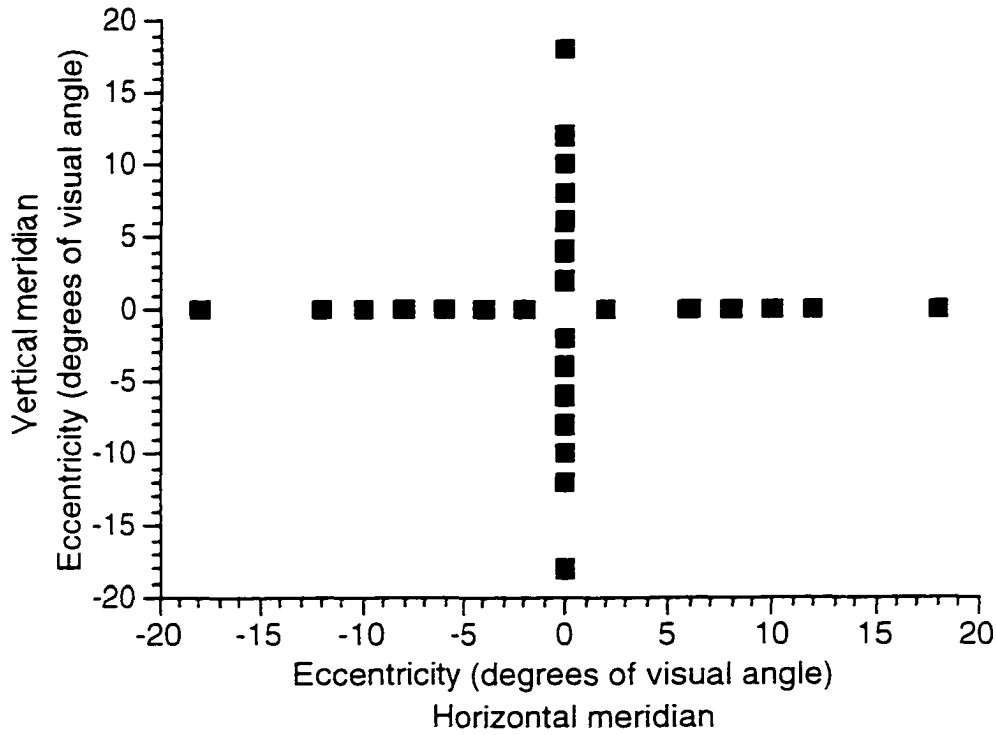

Figure 3. Photopic and scotopic sensitivity test loci. The central 32° of the visual field was tested on the horizontal and vertical meridian at 14 loci each.

Scotopic Visual Field Sensitivity

Scotopic testing was performed with a modified HFA. We made several modifications to the HFA that permit the perimeter to be operated under scotopic conditions (Chen et al., 1992; Jacobson et al., 1986). To allow for the monitoring of fixation during scotopic testing, the HFA was equipped with an infrared CCD camera and an infrared light source to illuminate the bowl. An additional motorized filter wheel was installed in the HFA's light path. The filter wheel was controlled remotely from the external microcomputer with a Lab-NB data acquisition board (National Instruments Corp., Austin, TX). The filter wheel allows for the addition of 7 standard-size optical filters, which allows for the rapid change of stimulus wavelength in the HFA. The HFA's light source was baffled to eliminate light leakage from its internal light source. The monitor of the HFA was modified by adding a red screen to eliminate monitor glow. In addition, a curtain between the subject and experimenter shielded the subject from any remaining light emitted from the monitor.

After the photopic test, the lights in the room and the background lighting in the HFA were extinguished. The subject was dark-adapted for 40 min before the scotopic measurements were begun. The same test pattern was used as above. The stimulus was a 500-nm (Ealing # 35-3508, FWHM 7.4, Peak 50%), Goldmann size V (1.7° visual angle), circular test spot. The stimulus duration was 200 msec. The HFA's full threshold strategy uses a modified 4-2 staircase threshold strategy (Cornsweet, 1970). The subject was instructed to focus on a red LED fixation light in the center visual field. The subject

responded that the stimulus was seen by pushing a button. Subjects that exhibited an average sensitivity less than 30 dB were excluded from the study.

Lens Density Estimation

The aging-related effect of lens density is a major obstacle in the study of night vision and aging. A perimetry-based method to estimate lens density was performed by comparing the difference of scotopic spectral sensitivity and the absorption spectrum of rhodopsin. This method requires very little time and was more sensitive to individual differences in lens density. Sample et al. (1988) described the following method to estimate an individual's lens density by scotopic perimetry. Because the action spectrum of rhodopsin does not change with age, an estimate of lens density can be obtained by measuring scotopic sensitivity at a location outside the macula for 2 wavelengths of equal rhodopsin sensitivity. If no absorption was present, the scotopic sensitivity of the subject should be equal for the 2 wavelengths. Light absorption by the lens is wavelength dependent so that shorter wavelengths are preferentially absorbed. The difference in sensitivity between the 2 wavelengths is the amount of light absorbed by the lens. With increasing lens density, the difference in scotopic sensitivity between the longer wavelength and shorter wavelength becomes larger. This estimate of lens density is called the lens density index (LDI) by Sample et al. The LDI is calculated as shown in Equation 1: LDI = (log 560-nm threshold - log 410-nm threshold) - radiance difference. Sample, Esterson, & Weinreb (1989) validated this lens density estimate with a custom-built perimeter and a HFA. Sample et al.'s (1988) LDI is robust to age-related rod loss or

scotopic sensitivity loss because this loss would affect sensitivity for the two wavelengths equally. The rate of lens density increase found as a function of age was comparable to that found by Said and Weale (1959) using a photometric technique. The LDI was used to correct dark-adapted thresholds for the effect of lens density. The correction formula (Equation 2) was based on the data of Wyzecki and Stiles (1986): Corrected Threshold = Measured 500 nm Threshold ÷ ((LDI * (500 nm Lens Density / (410 nm Lens Density - 560 nm Lens Density))) /0.1).

Using Sample et al.'s (1988) method, the pair of wavelengths for testing are produced by 410-nm and 560-nm standard band pass filters (410 nm Ealing # 35-3243, FWHM 9.7, Peak 45%; 560 nm Ealing # 35-3706, FWHM 9.4, Peak 50%). A Goldmann size V target (1.7° of visual angle) located 15° in the nasal visual field was used for the lens density estimation. Two thresholds were measured for each of the two filters, using the threshold procedure outlined below.

The HFA was controlled from a custom-written application (Jackson, 1997) running on an external microcomputer. The program on the external microcomputer determined the threshold and controlled the sampling rate of threshold measurement. The program used a modified 3-1 single staircase threshold strategy to determine threshold. For the initial threshold, the stimulus intensity started at 30 dB. If the subject did not respond to the stimulus, the stimulus intensity stepped 10 dB brighter. When the subject responded that the stimulus was superthreshold, the stimulus intensity became 3 dB dimmer. When the subject responded that the stimulus was subthreshold, the stimulus intensity was increased by 1 dB until the subject responded that the stimulus was visible,

and that stimulus intensity was recorded as a threshold. Successive threshold measurements start with a stimulus intensity 5 dB below the previous threshold measurement. The test-retest for each threshold determination must be within 4 dB in order for the thresholds to be considered valid. If the difference between the first and second threshold was greater than 4 dB, the computer retested the point starting at an intensity 5 dB brighter than the last recorded threshold.

Dark Adaptation

Several methodological flaws found in the previous literature on dark adaptation and aging were corrected in this study. The present study used a higher sampling rate of threshold measurements in order to more accurately estimate the dark adaptation function compared with previous studies (Birren & Shock, 1950; McFarland et al., 1960). The time to reach baseline dark-adapted sensitivity was measured. The time to baseline is an acceptable method to indirectly measure the rate of rod adaptation. For each subject, a baseline measurement of the final dark-adapted sensitivity was measured. The amount of time to reach a threshold 3 dB above baseline threshold during dark adaptation was recorded. The 3-dB cushion was provided to cope with noise in the individual and the measuring instrumentation. The cushion also shortened the length of test time for subject comfort. Furthermore, a flash bleach that attained a 98% bleach was used. McFarland et al. used a bleach that achieved less than a 50% bleach. A larger bleach may expose alterations in the slowed kinetics of dark adaptation not apparent with less taxing bleaches. In addition to the rod-cone break and the duration of dark adaptation, several

parameters of the dark adaptation kinetics not previously examined in aging research were quantified. The slopes of the second component (rhodopsin regeneration) and the third component of the dark adaptation curve were quantified. These slopes correspond to time constants that give insight into the underlying mechanism of dark adaptation (Lamb, 1981; Leibrock et al., 1994; Stabell et al., 1992) Each slope is thought to represent a different portion of rhodopsin regeneration pathway. The dark adaptation kinetics that were measured are shown in Figure 1.

Subjects' dark adaptation was measured using the same HFA as previously described. The target stimulus was a 500-nm Goldmann size V (1.7° of visual angle) circular target located at 12° inferior visual field on the vertical meridian. The target wavelength and location were chosen for several reasons. The wavelength of the stimulus was chosen because 500 nm is near the peak of rod sensitivity, which was of the primary interest of this project. In part, the stimulus parameters were chosen because the HFA has a software-imposed limited range of stimulus intensities (0 dB to 60 dB). The wavelength and location of the stimulus provided an adequate range of stimulus intensities to avoid a ceiling or floor effect. The subject was bleached using a flash bleach (Sunpak 622 Super). The intensity of the flash was calculated to be 7.65 log scotopic trolands, producing a ~ 98 % bleach. After the flash bleach, threshold measurements were initiated by the external computer. The following threshold sampling strategy was used. Thresholds are measured twice every min for the first 25 min. After the 25th min, thresholds were measured twice every 2 min until the end of the session. Dark

adaptometry was terminated when the subject reached within 3 dB of their baseline sensitivity or a total of 90 min elapsed.

The threshold strategy for dark adaptometry was slightly modified from the threshold strategy used for lens-density estimation. For the initial threshold, the stimulus intensity started at 0 dB. If the subject did not respond to the stimulus, the stimulus intensity remained at 0 dB until the subject responded that the stimulus was seen. When the subject responded that the light was visible, the threshold intensity was decreased by 3 dB steps until threshold was crossed. After the subject responded that the stimulus was not visible by not pressing the response button, the intensity of the stimulus was increased by 1 dB until the subject responded that the stimulus was visible, and the stimulus intensity was recorded as the threshold. Successive threshold measurements started with a stimulus intensity 3 dB brighter than the previous threshold measurement.

Recent advances in the modeling of dark adaptation necessitated an objective method to quantify dark adaptation kinetics. This project was the first to develop a non-linear regression technique that rapidly analyzes large sample datasets and allows us to evaluate objectively several models of dark adaptation simultaneously (McGwin, Jackson, & Owsley, 1998). Using a nonlinear regression technique has two main advantages. The first advantage is that the transition times and rate constants of the model are fitted simultaneously. Generally, this approach produces a fit that better describes the data compared with a technique that fits the function in a stepwise manner. Second, nonlinear regression techniques are advantageous because they allow for the use

of untransformed data. Thus, the estimated dark-adaptation kinetics are in meaningful units and reflect the actual rate of sensitivity recovery. The nonlinear regression was fitted to the threshold measurements as a function of time. Two models of dark adaptation were evaluated. The first model was a three-component piecewise linear model (Equation 3): Threshold = (threshold intercept + slope cone recovery * time) + slope of 2nd component * (time - rod-cone break) + slope of 3rd component * (time - rod break). This model is a representation of the physiological model of Lamb (1981). Essentially, this model isolates the second and third components of dark adaptation and calculates their respective rates of recovery. The second model was a four-component piecewise linear model (Equation 4): Threshold = (threshold intercept + slope of initial cone recovery * time) + slope of cone plateau * (time - cone inflection point) + slope of 2nd component * (time - rod-cone break) + slope of 3rd component * (time - rod break). This model was chosen because it appears to fit the cone portion of the dark adaptation data more accurately than the three-component linear model. Although the cone data were not of interest, a better overall fit of the data was essential to accurately fit the rod data. For the two models, we estimated the rod cone break, rod break, slope of the second component, slope of the third component, and R^2 statistics to evaluate how well the model fit the data. Using the SAS System (SAS Institute, 1997), we estimated these parameters using the NLIN procedure. The SAS program is listed in Appendix B.

Questionnaires

A standardized interview assessing the medical conditions of the subjects was given. The purpose of the questionnaire was to characterize the general health of the sample. The medical conditions questionnaire was developed in our laboratory for the impact of cataracts on mobility study (Owsley, Stalvey, Wells, & Sloane, unpublished). For each of the 17 health conditions or symptoms, subjects were asked if they currently had that health problem or symptom. In addition, subjects were asked if they had any acute illnesses or other illnesses at the time testing. If subjects had the condition or symptom, they were asked if they were bothered a little, a lot, or a great deal; this produced a score of 1-3, respectively, for each condition. Comorbidity was calculated for each subject by adding the score for all of the conditions.

A standard medication inventory was taken on each subject as well. In addition to prescription medications, each subject's use of vitamins and nutritional supplements was quantified. The medications and nutritional supplements were inventoried to determine whether any of the subjects were taking medications that would affect their dark adaptation, such as large doses of vitamin A. The medication inventory was used in the impact of cataracts on mobility study (Thomas, Owsley, Stalvey, & Panizzi, 1997). Subjects indicated the type and dosage of any medications or nutritional supplements they were taking at the time of testing.

Macula Grading Scale

In order to document the retinal health of the subjects at the time of testing, fundus photos of the subjects over age 49 was made. The prevalence of retinal disease, especially ARM, increases in the later decades of life (Leibowitz et al., 1980; Tielsch, Sommer, Witt, Katz, & Royall, 1990). Previous studies of aging and dark adaptation have not objectively documented the retinal health of the old adults. Thus, it is unclear to what extent the aging-associated alterations in dark adaptation reported in earlier studies reflect retinal pathology and to what extent they would exist even in those old adults with no or minimal signs of retinal disease.

Following dark adaptometry, stereo fundus photographs were made for the tested eye on all subjects over 50 years old. Photographs were made with the center of focus on the optic disk and posterior pole (FF4 fundus camera, Zeiss, Inc., Germany). They were evaluated through the use of a macular grading scale based on the international classification and grading system described by Bird et al. (1995) and those described by Klein et al. (1991) and Chuang & Bird (1988). The stages of the grading scale are listed in Table 1. Similar to the international classification and grading system, the presence of 1 or more large druse ($\geq$ 63 μm), focal hyperpigmentation, or both indicates a classification of stage 2 and a diagnosis of ARM. The presence of only small hard drusen classifies the subject as being normal. The presence of geographical atrophy, choroidal neovascularization, or both marks the more severe stages of the scale. Photographs were rated by an experienced grader who did not know the ages, clinical characteristics, or psychophysical results of subjects.

RESULTS

The sample consisted of 94 subjects whose demographics are listed in Table 2. The results are organized into the following sections: visual functional assessment, lens density estimation, photopic visual field, scotopic visual field, dark adaptometry, and macula grading scale. To examine whether dark adaptation parameters decline with increasing age, for each dependent variable of interest, a Pearson correlation was performed. The r statistic, F statistic, and p value are reported for each test. For comparisons to previous reports that compared young adults and old adults, the adults were also grouped into 2 age groups, young and old. The young group consisted of adults 20-39 years old. The old group consisted of adults 60 years old and older. A one-way ANOVA was performed comparing these two age groups for each dependent variable of interest. A p value < 0.05 was considered significant.

Visual Function Assessment

For each decade, the contrast sensitivity and acuity measured under photopic conditions are listed in Table 3 for the eye tested psychophysically. Best-corrected distance acuity declined with age ($r = 0.45$, $F[1, 92] = 23.24$, $p < 0.0001$). The young adults' average acuity of -0.2 LogMAR ($SD = 0.07$, ~20/15) was better than the old adult's average acuity of -0.01 LogMAR ($SD = 0.08$, ~20/20, $F[1, 62] = 13.21$, $p < 0.0006$). Contrast sensitivity for large letters as displayed on the Pelli-Robson chart also

declined with age (r = 0.52, F[1,92] = 33.34, p < 0.0001). The old adults had lower contrast sensitivity (M = 1.56, SD = 0.10) compared with young adults (M = 1.74, SD = 0.13, F[1,62] 37.19, p < 0.0001) consistent with earlier work on old adults in relatively good eye health (Elliott, Sanderson, & Conkey, 1990; Jackson et al., in press).

Table 2
Subject Demographics

Age	Number	Gender		Race		
		Female	Male	Caucasian	African American	Other
20s	10	8	2	8	1	1
30s	8	5	3	7	1	0
40s	10	8	2	10	0	0
50s	20	11	9	19	1	0
60s	21	9	12	18	3	0
70s	17	9	8	16	1	0
80s	8	5	3	8	0	0
Total	94	55	39	86	7	1

Table 3
Acuity and Contrast Sensitivity by Decade

Measure		Age group						
		20s	30s	40s	50s	60s	70s	80s
Acuity[1]	*M*	-0.90	-0.10	-0.08	-0.08	-0.42	-.01	0.04
	SD	.076	0.07	0.10	0.06	0.10	0.06	0.06
Contrast sensitivity[2]	*M*	1.72	1.78	1.71	1.68	1.61	1.50	1.55
	SD	0.13	0.14	0.13	0.17	0.09	0.09	0.09

[1]logMAR
[2]log contrast sensitivity

Lens Density Estimation

The LDI increased with decade at a rate of 0.12 LDI/decade (Figure 4; $r = 0.48$, $F[1,92] = 27.92$, $p < 0.0001$). Old adults had a greater LDI ($M = 1.20$, $SD = 0.47$) compared with younger adults ($M = 0.64$, $SD = 0.29$, $F[1,62] = 19.60$, $p < 0.0001$). The reported LDI values are consistent with the previous literature and previous findings in our laboratory (Jackson et al., in press; Sample et al., 1988). The lens density correction factor of the scotopic thresholds were calculated for each subject as detailed in Method above. The average lens density correction factor for the 500-nm test target was 0.64 dB ($SD = 0.29$) for the young adults and 1.16 dB ($SD = 0.47$) for the old adults. Unless specified otherwise, all reported scotopic thresholds are corrected for lens density. As mentioned earlier, the scotopic thresholds below were corrected by adding the 500-nm correction factor to the sensitivity.

Photopic Visual Field

The average threshold at each of the 28 test loci comprising the visual field were averaged together to calculate the mean photopic sensitivity for each subject. In general, the mean photopic sensitivity decreased as a function of decade at a rate of 0.54 dB/decade ($r = 0.52$, $F[1, 92] = 35.56$, $p < 0.0001$). Old adults exhibited an average photopic sensitivity decline of 2.22 dB compared with young adults ($F[1, 62] = 22.82$, $p < 0.0001$; Figure 5). Old adults exhibited a mean photopic sensitivity of 20.57 dB ($SD = 1.47$) compared with 22.79 dB ($SD = 2.13$) for young adults. The old adults' sensitivity loss was greater

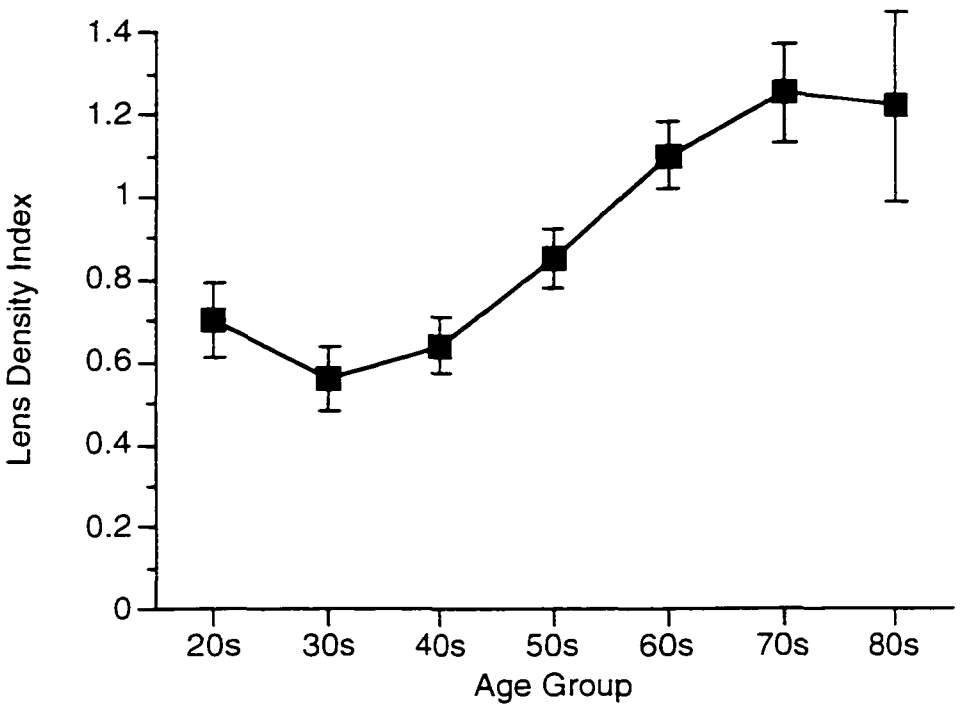

Figure 4. Mean Lens Density Index as a function of decade. Error bars are ± 1 standard error of the mean.

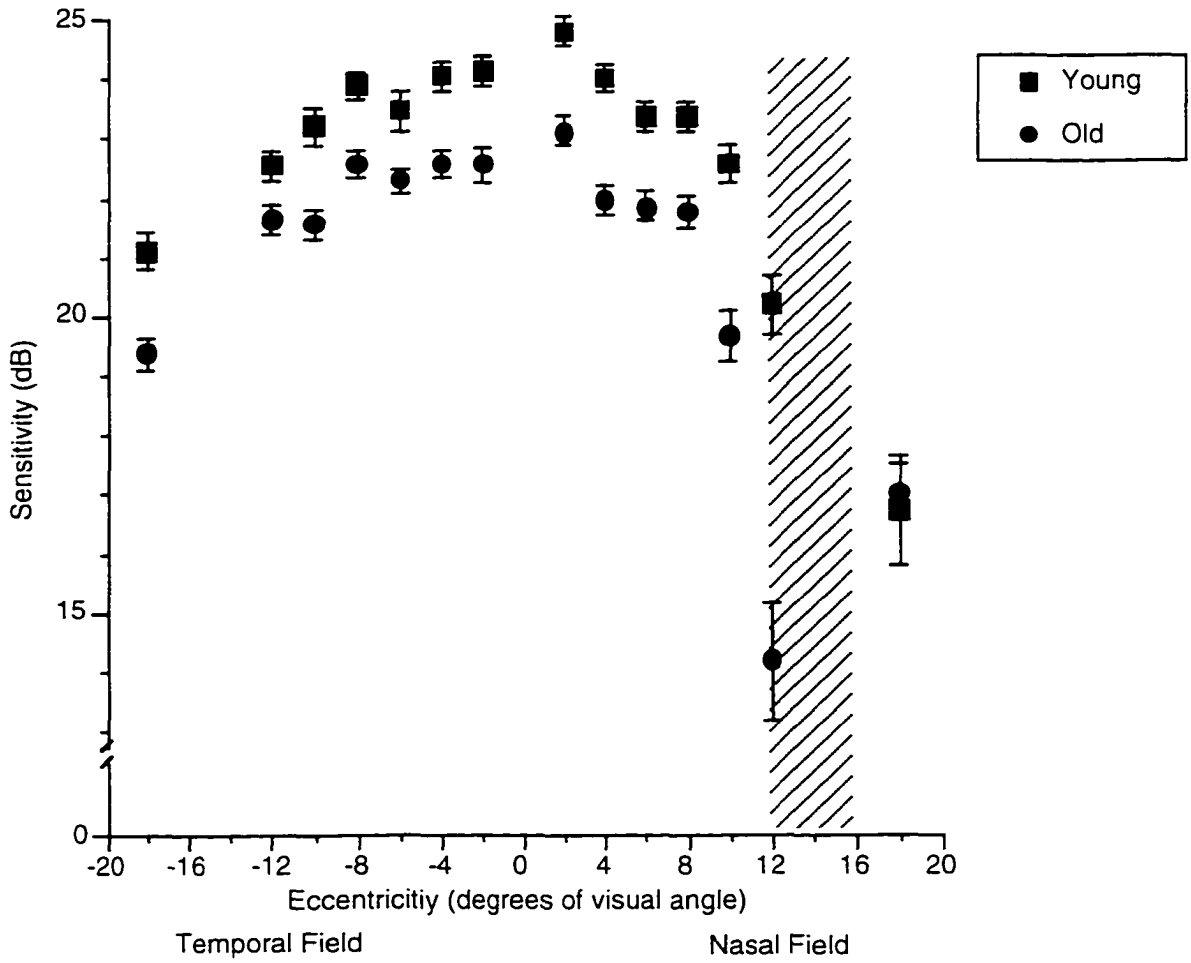

Figure 5. Mean photopic sensitivity along the horizontal meridian of the visual field. Error bars are ± 1 standard error. The old adults' increased sensitivity loss at 12° is probably because of peripapillary chorioretinal atrophy (Curcio, Saunders, Younger, Medeiros, & Millican, 1996). Old adults sensitivity loss did not change with eccentricity.

in the temporal visual field (2.21 dB) than the nasal visual field (0.14 log units: $F[1, 72] = 7.38, p < 0.008$).

Scotopic Visual Field

As with the photopic field, the mean scotopic sensitivity was calculated by averaging the 28 points of the visual field for each subject. Mean sensitivity lens density corrected for adults declined at a rate of 0.86 dB/ decade ($r = 0.53$, $F[1, 92] = 34.94$, $p < 0.0001$). Old adults exhibited on average a 0.33 log unit loss in sensitivity at all retinal loci tested ($F[1, 62] = 20.21$, $p < 0.001$; Figure 6) and is consistent with earlier work (Jackson et al., in press; Sturr et al., 1997). The old adults' sensitivity loss was greater in the temporal visual field (0.36 log unit) than the nasal visual field (0.25 log unit; $F[1, 72] = 7.38$, $p < 0.008$).

Dark Adaptation

A nonlinear regression technique was used to fit a three-component linear model (Equation 3) and a four-component linear model (Equation 4) to each individual's dark adaptation data. The four-linear component model was chosen over the three-linear component model because it was an improved fit of adults' sensitivity recovery, especially the cone-mediated portion ($Z = 2.74$, $p < 0.004$). It was essential to accurately fit the cone-mediated portion of the data in order to more accurately estimate the rod kinetics in an unbiased manner. For the four-linear component model, the first linear component accounted for the initial threshold elevation, and the second linear component described the cone plateau. The next linear component described the second component

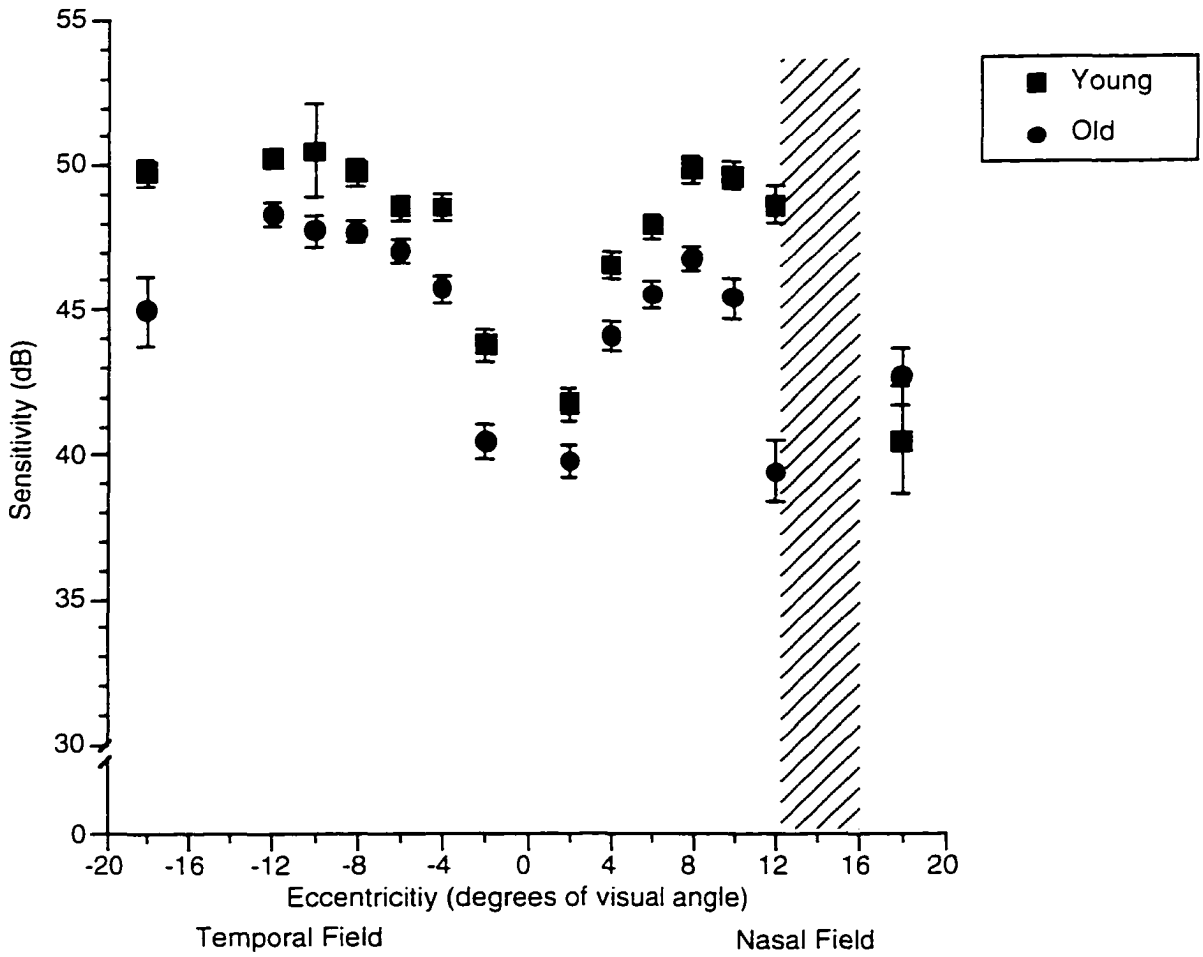

Figure 6. Mean scotopic sensitivity along the horizontal meridian of the visual field. Error bars are ± 1 standard error of the mean. The old adults' increased sensitivity loss at 12° is probably because of peripapillary chorioretinal atrophy (Curcio, Saunders, Younger, Medeiros, & Millican, 1996). Old adults' scotopic sensitivity loss was greater in the temporal visual field.

of rod-mediated sensitivity recovery. The last linear component accounted for third component of rod-mediated sensitivity recovery. For each of the 94 adults, individual estimates were made of the rod-cone break, the rod transition time, the second component (rhodopsin regeneration), and the third component. The baseline threshold and time to baseline were also recorded. Table 4 lists the mean estimates across adults for each decade. For purposes of illustration in Figure 7, adults' individual data were grouped by decade and fitted with the four-component linear model to produce nonlinear regression functions for each decade. A detailed description of the results for each of the dark adaptation kinetic estimates follows.

Table 4
Dark Adaptation Kinetics

Dark adaptation parameter		Age						
		20s	30s	40s	50s	60s	70s	80s
Rod-cone break (min)	*M*	13.56	13.70	13.32	14.98	14.65	16.00	17.69
	SD	1.22	1.37	1.23	2.13	1.72	2.52	2.29
2nd component (dB/min)	*M*	2.73	2.35	2.72	2.29	2.06	2.13	2.06
	SD	0.69	0.50	0.33	0.45	0.49	0.38	0.59
Rod break (min)	*M*	21.27	21.66	21.36	24.54	26.20	26.78	29.67
	SD	1.43	2.57	1.24	2.79	3.51	2.60	3.21
3rd component (dB/min)	*M*	0.61	0.58	0.49	0.46	.38	0.43	0.28
	SD	0.23	0.22	0.15	0.17	.18	0.19	0.13
Baseline sensitivity (dB)	*M*	51.47	51.07	48.59	49.58	48.62	48.63	46.13
	SD	2.14	1.88	2.25	1.76	2.52	2.37	3.72
Time to baseline (min)	*M*	35.31	36.55	40.81	42.78	47.69	46.19	48.22
	SD	7.43	4.66	6.90	42.78	7.34	8.17	6.12

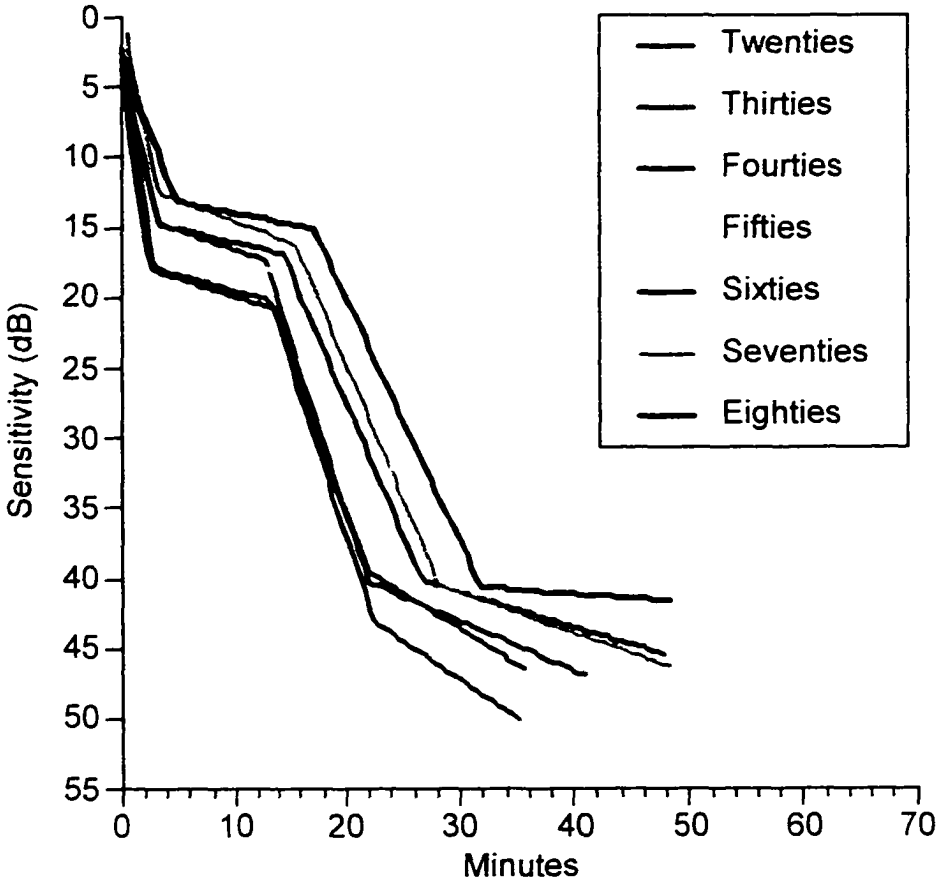

Figure 7. Dark adaptation as a function of decade. The adults' individual data were grouped by decade and fitted with the 4-component linear model. The resulting equations from the nonlinear regression analysis were plotted for illustration purposes. Note that the functions shift to the right with increasing decade, indicating a slowing of the rate of dark adaptation. Each age group's function is terminated at the group's mean time to baseline.

Rod-cone break. The rod-cone break represents the point in time during dark adaptation that the recovering rods' sensitivity surpasses the cones' sensitivity. The rod-cone break increases with age at a rate of 0.65 min/decade ($r = 0.49$, $F[1, 92] = 28.27$, $p < 0.0001$; Figures 8 and 9). Old adults have an average rod-cone break of 15.76 min ($SD = 2.35$) compared with 13.64 min ($SD = 1.34$) for young adults ($F[1, 62] = 13.03$, $p < 0.0006$).

Second component. As mentioned earlier, the slope of the second component of dark adaptation is an indirect measurement of the rate of rhodopsin regeneration that may be dependent on translocation of 11-*cis* retinal from the retinal pigment epithelium to the rod outer segment (Lamb et al., 1997). Sensitivity recovery during the second component of dark adaptation decreased with age at a rate of 0.15 dB/decade ($r = 0.44$, $F[1, 92] = 22.37$, $p < .0001$; Figures 10 and 11). The old adults exhibited an average second component slope of 2.10 dB/min ($SD = 0.44$) compared with the young adults' average slope of 2.64 dB/min ($SD = 0.56$; $F[1, 62] = 16.20$, $p < 0.0002$).

Third component. The third component of dark adaptation is the phase that begins at the rod break and terminates at the time that baseline sensitivity is obtained. The rate of recovery during the third component may be rate limited by the recycling of retinoid in the retinal pigment epithelium. Sensitivity recovery during the third component of dark adaptation decreased with age at a rate of 0.05 dB/decade ($r = 0.44$, $F[1, 92] = 22.52$, $p < 0.0001$; Figures 12 and 13). The rate of the sensitivity recovery is much slower for the third component than the second component. Old adults exhibited

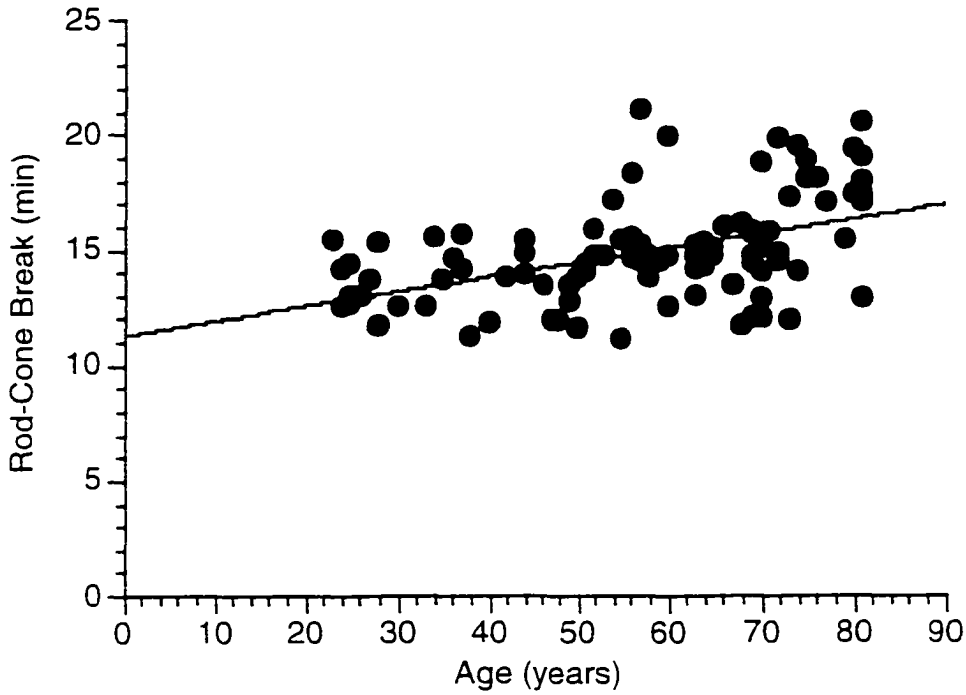

Figure 8. Rod-cone break as a function of age. The rod-cone break increases at a rate of 0.65min/decade.

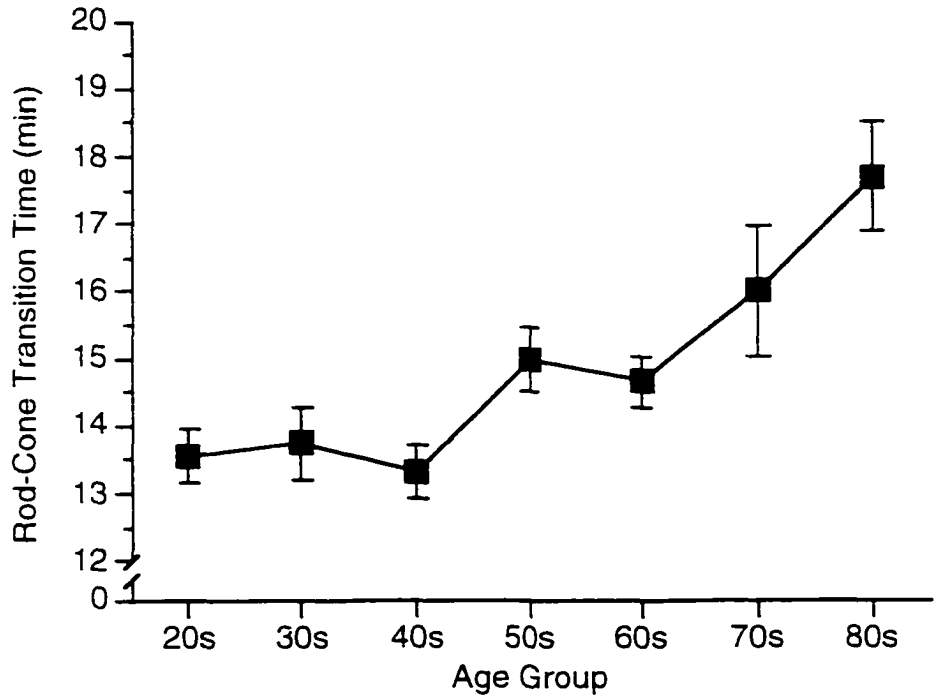

Figure 9. Rod-cone break as a function of decade. Error bars are ± 1 standard error of the mean.

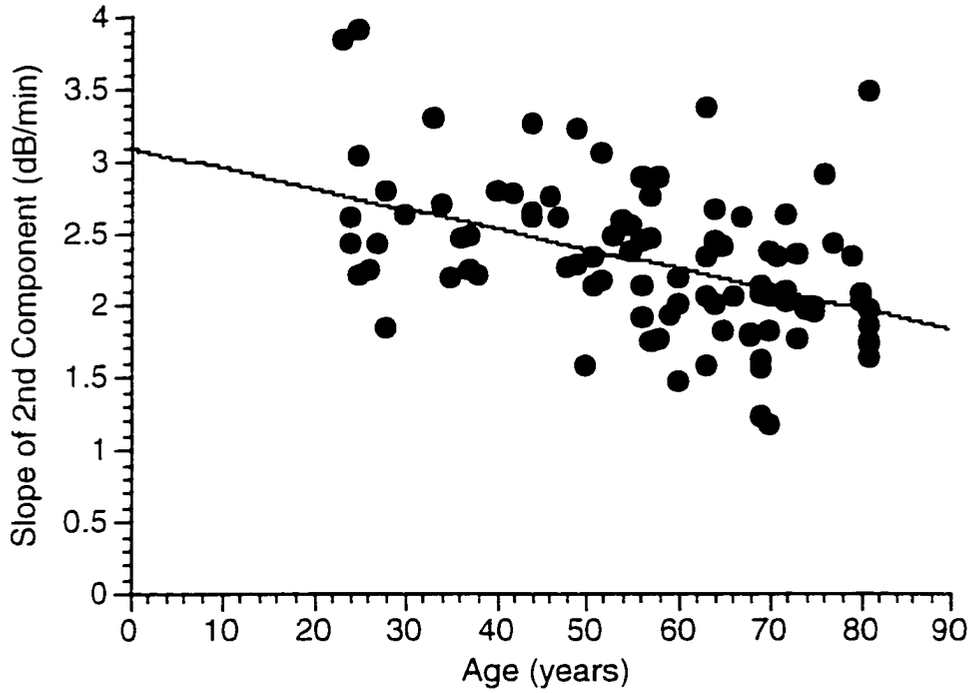

Figure 10. The slope of the second component of dark adaptation as a function of age. The slope of the second component of dark adaptation decreased at a rate of 0.15 dB/decade.

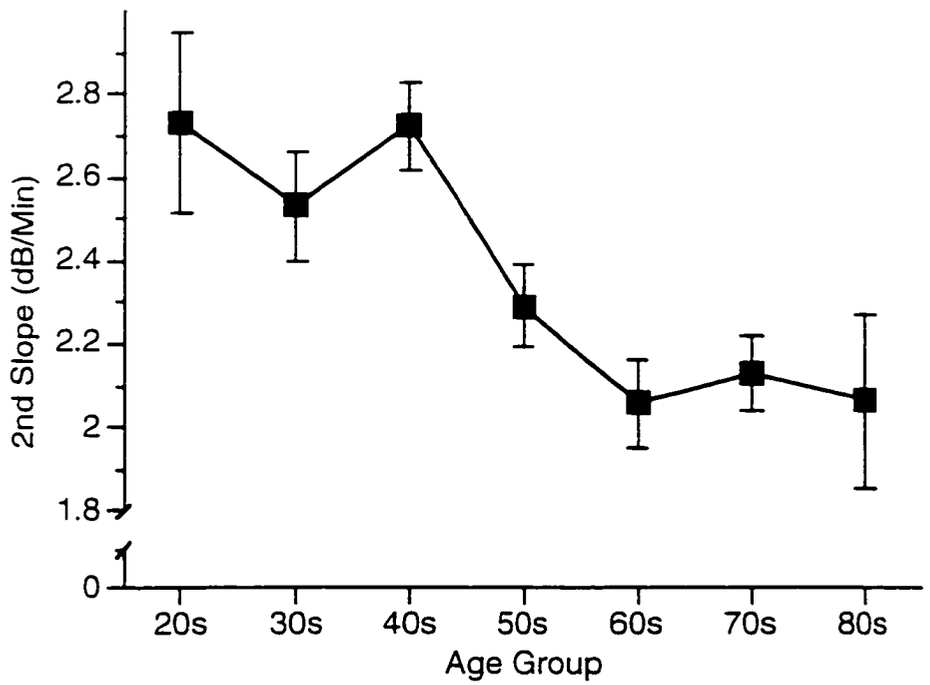

Figure 11. The slope of the second component of dark adaptation as a function of decade. Error bars are ± 1 standard error of the mean.

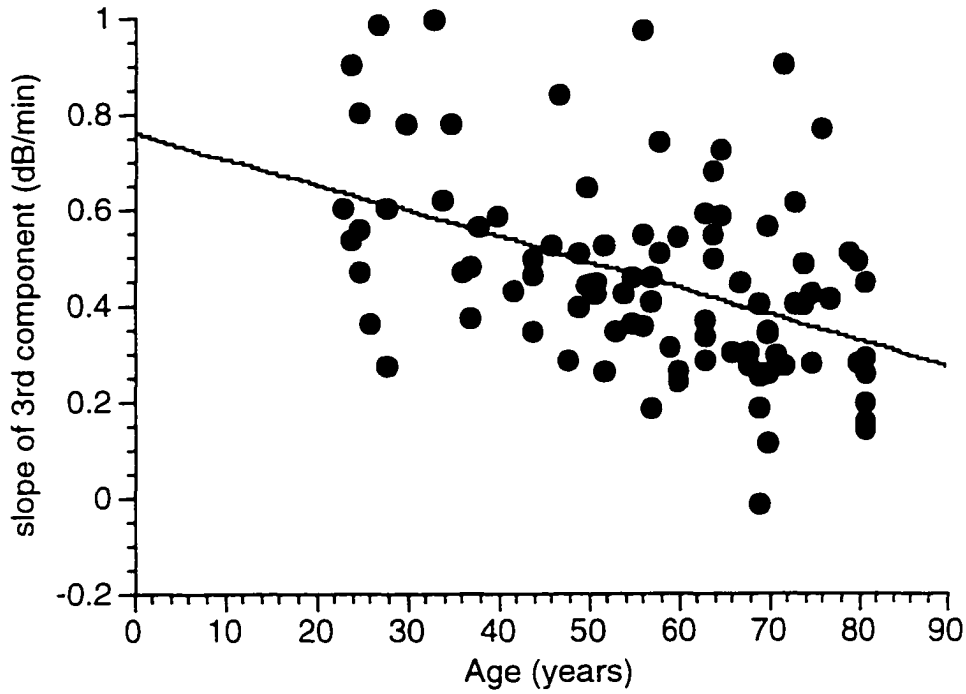

Figure 12. Slope of the third component of dark adaptation as a function of age. The slope of the third component decreased at a rate of 0.05 dB/decade.

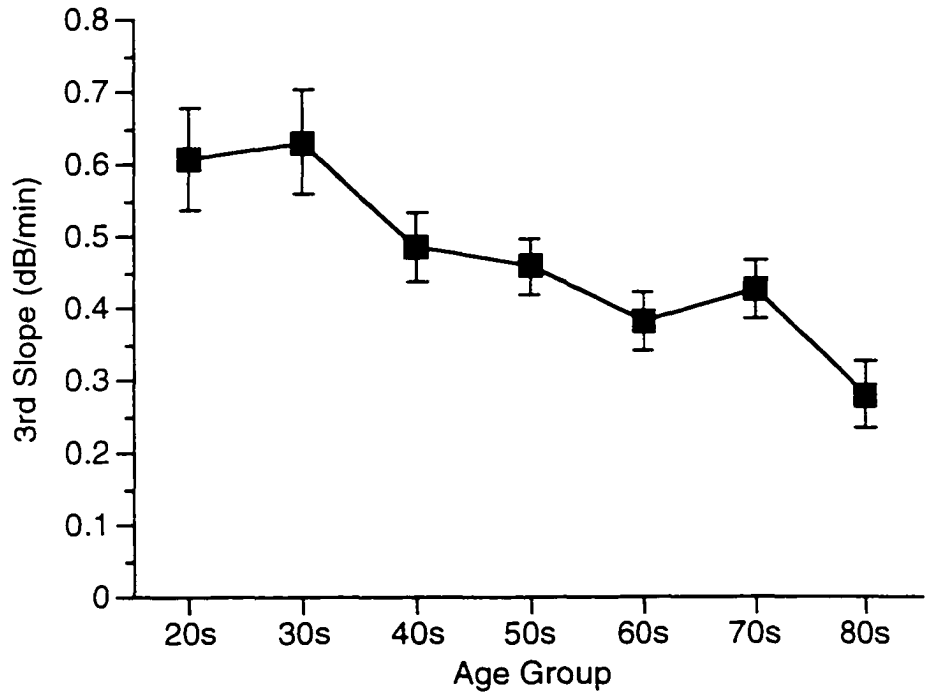

Figure 13. Slope of the third component of dark adaptation as a function of decade. Error bars are ± 1 standard error.

an average sensitivity recovery of 0.38 dB/min (SD = 0.18) compared with an average sensitivity recovery of 0.62 dB/min (SD = 0.21) exhibited by the young adults (F[1, 62] = 19.34, $p < 0.0001$). Even during this slower phase of sensitivity recovery, the old adults rate of recovery was 0.19 dB/min less than that of young adults.

Rod break. The time during dark adaptation that the third component of sensitivity recovery became apparent was defined at the rod break. The rod break represents the time that sensitivity recovery becomes mediated by the third component rather than the second component. The rod break increased with age at a rate of 1.50 min/decade (r = 0.68, F[1, 92] = 78.32, $p < 0.0001$; Figures 14 and 15). The rod break occurred on average 5.77 min later in the old group than the young group. The old adults' rod break became apparent at 26.95 (SD = 3.32) min compared with 21.18 (SD = 1.91) min for the young adults (F[1, 62] = 47.89, $p < 0.0001$).

Time to baseline. The time to baseline sensitivity was defined as the duration of time until the subject reached within 3 dB (0.3 log unit) of their baseline scotopic sensitivity. With age, the time to baseline increased 2.76 min/decade, r = 0.58, F(1, 92) = 46.19, $p < 0.0001$. (Figure 16 and 17)). Young adults reached baseline sensitivity about 12 min faster than the old adults. Old adults' average time to baseline sensitivity was 47.41 (SD = 7.32) min and 35.28 (SD = 6.18) min for the young adults, F(1, 62) = 38.58, $p < 0.0001$.

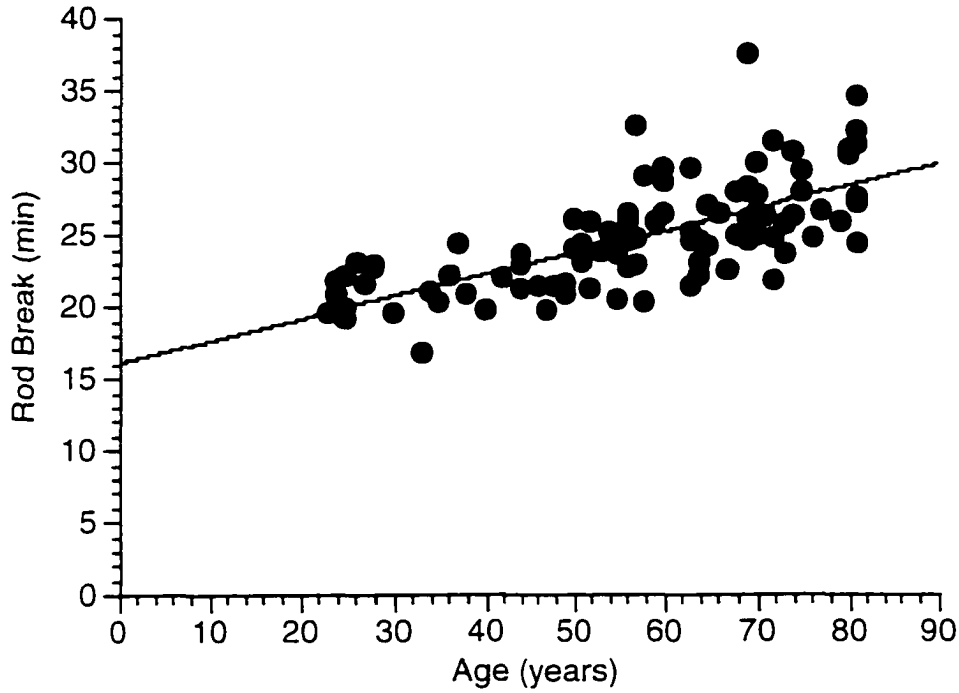

Figure 14. Rod break as a function of age. Rod break increased at a rate of 1.50 min/decade.

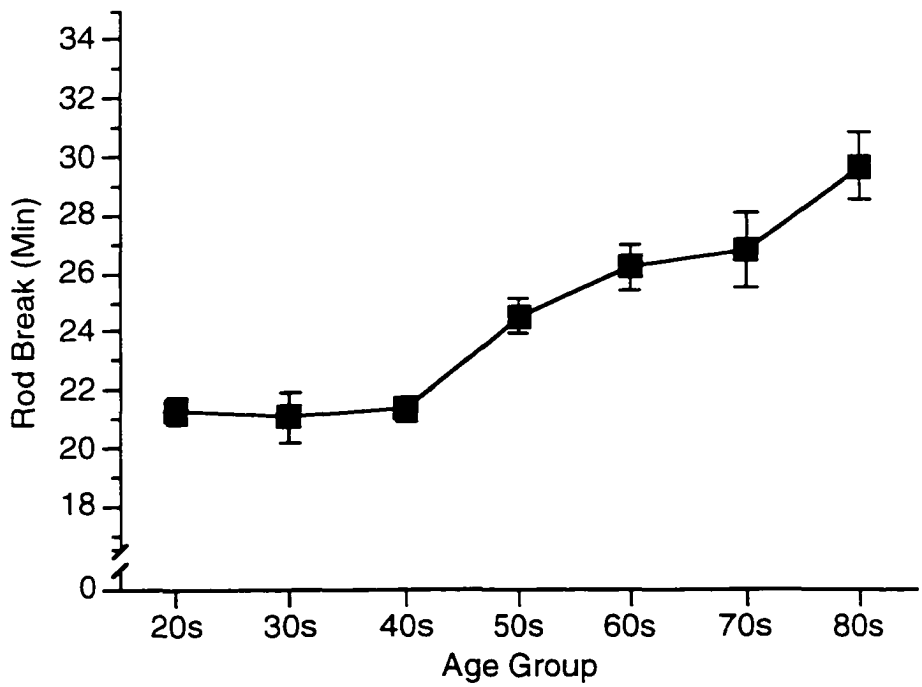

Figure 15. Rod break as a function of decade. The error bars are ± 1 standard error of the mean.

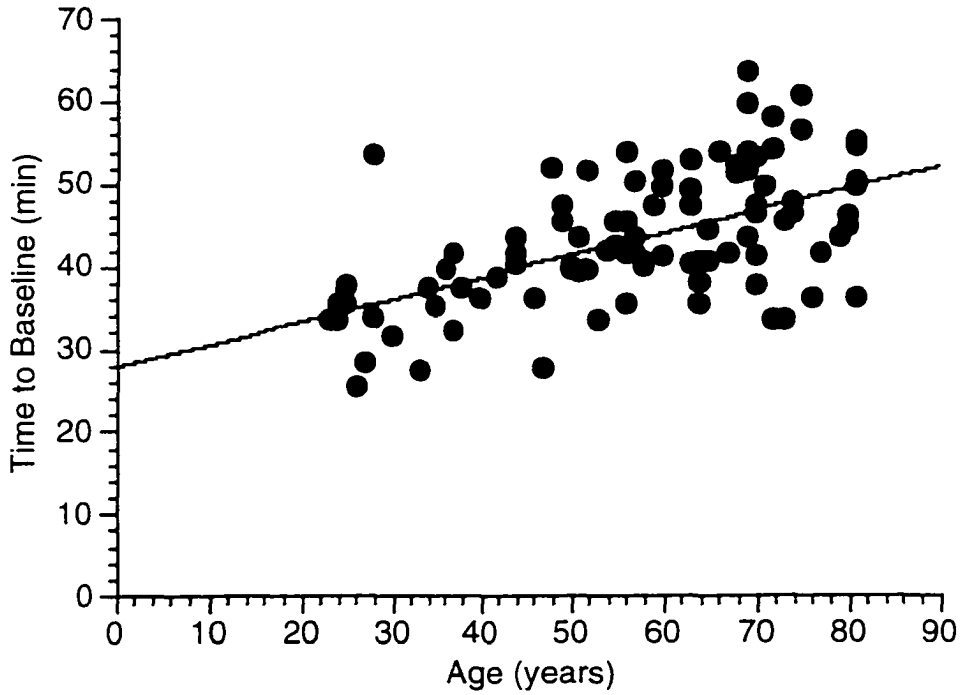

Figure 16. Time to baseline as a function of age. The time to baseline increased at a rate of 2.76 min/decade.

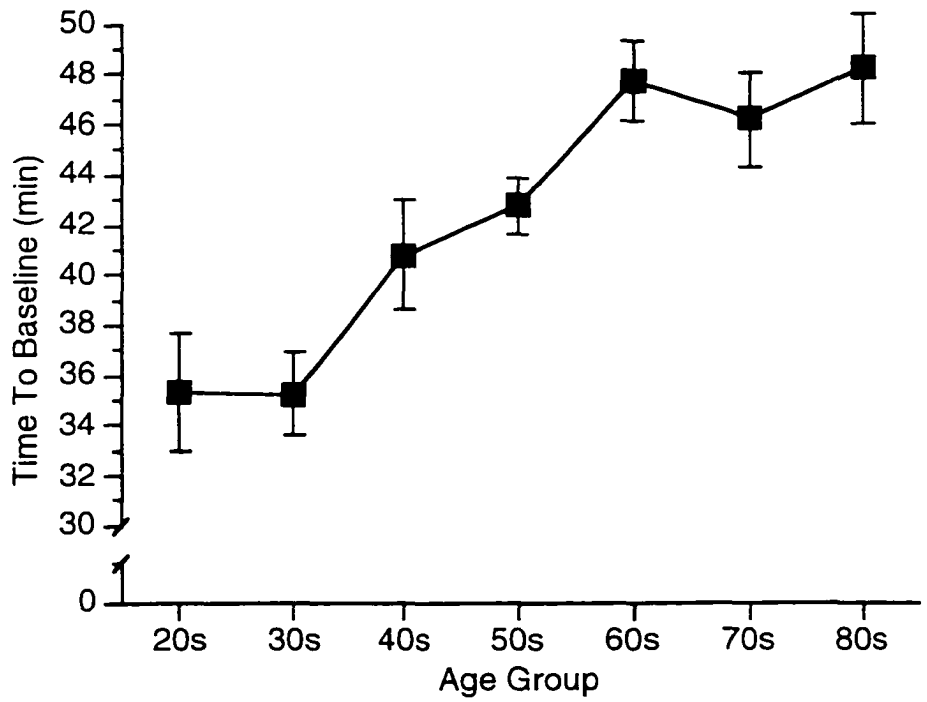

Figure 17. Time to baseline as a function of decade. Error bars are ± 1 standard error of the mean.

Baseline sensitivity. Baseline sensitivity decreased with age at a rate of 0.66 dB/decade ($r = 0.44$, $F[1, 92] = 21.33$, $p < 0.0001$; Figure 18). The old adults' mean sensitivity was about 2.10 dB less compared with younger adults. The baseline sensitivity of the old adults was 48.21 ($SD = 2.83$) compared with 51.21 ($SD = 2.05$) for the young adults ($F[1, 62] = 16.74$, $p < 0.0001$).

Questionnaires. The number of self-reported health conditions reported by the adults increased with age ($r = 0.50$, $F[1, 92] = 30.87$, $p < 0.0001$). Older adults reported an average of 1.63 ($SD = 1.27$) conditions compared with 0.22 ($SD = 0.43$) conditions for the younger adults ($F[1, 62] = 20.97$, $p < 0.0001$). Comorbidity score increased with age ($r = 0.39$, $F[1, 92] = 16.29$, $p < 0.0001$). Old adults' comorbidity score was on average 2.65 ($SD = 2.51$) compared with an average 0.44 ($SD = 0.87$) for young adults ($F[1, 62] = 13.17$, $p < 0.0006$). The frequency of the specific health conditions and symptoms reported by the adults are listed in Table 5. The classification of the medications and dietary supplements taken by the adults are listed in Table 6 and Table 7, respectively. Old adults in the sample consumed more prescription medications for cardiovascular-related diseases compared with young adults, as expected. From the results of the medication inventory, the old adults were not taking prescription medications known to affect dark adaptation (Gottlob, Strenn, & Schneider, 1994; Rengstorff & Royston, 1976; Seppala, Korttila, Hakkinen, & Linnoila, 1976; Wirz-Justice et al., 1997). Vitamin usage among the adults were similar, regardless of age. None of the adults in the sample was taking unusually large amounts of vitamin A or antioxidants.

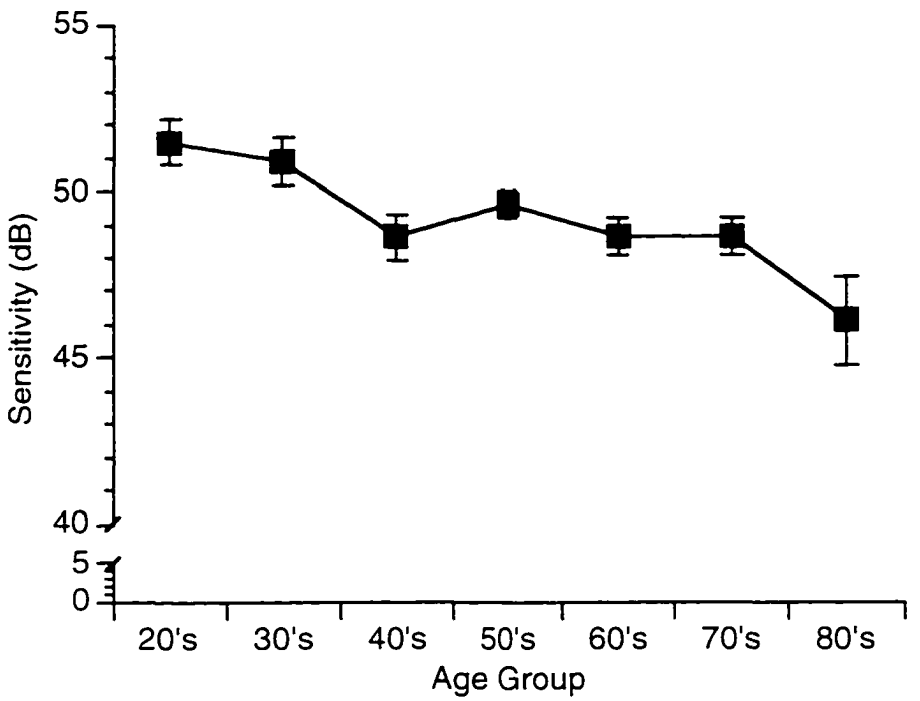

Figure 18. Baseline sensitivity as a function of decade. Error bars are ± 1 standard error of the mean. Baseline sensitivity decreased with decade at a rate of 0.66 dB/decade.

Table 5
Percentage of Self-Reported Medical Conditions by Age

	Age group						
Medical condition	20s	30s	40s	50s	60s	70s	80s
Heart	10	13	30	-	10	6	5
Circulation	-	-	-	10	5	18	5
High blood pressure	-	-	-	15	33	41	25
Low blood pressure	-	13	-	-	5	-	-
Neurological	-	-	-	-	-	-	-
Diabetes	-	-	-	5	-	12	10
Arthritis	-	13	10	30	24	53	15
Osteoporosis	-	-	-	10	10	12	5
Cancer	-	-	-	-	-	-	-
Chronic pulmonary problems	-	-	-	-	5	12	-
Digestion	-	-	-	10	14	12	10
Urinary	-	-	-	5	10	12	-
Kidney (other than infection)	-	-	-	-	5	-	-
Hearing impairment	-	13	-	15	5	24	15
Speech impairment	-	-	-	-	-	-	-
Vision impairment	10	-	-	-	-	-	-
Acute conditions	-	-	10	-	5	12	-
Other conditions	-	-	-	-	-	-	-

Macula Grading Scale. The recruitment of the adults for inclusion in the study was based on the clinical charts and a screening of their visual function in the laboratory on the day of testing. Although the sample was clinically normal, the grading scale classified 32% of the adults as having the earliest signs of ARM (stage 2). The frequency distribution of the macular grades is shown in Table 1. Of the 46 adults that were over 50 years old, 61% (28) received a grade of normal (0 or 1). A grade of 0 or 1 indicates that no signs of retinal changes associated with ARM are present. A macular grade of 2 was

Table 6
Percentage of Subjects Taking Prescription Medications by Age

	Decade						
Prescription medication	20s	30s	40s	50s	60s	70s	80s
Antibiotics	-	-	10	-	5	12	-
Anticoagulants	-	-	-	-	-	-	5
Antidepressants	20	-	-	10	5	6	-
Anti-inflammatory	-	-	10	10	-	6	-
Antilipemic drugs	-	-	-	10	-	12	10
Autonomic drugs	-	-	-	-	-	-	-
Cardiac drugs	-	-	-	-	19	6	20
Contraceptives	20	-	-	-	-	-	-
Diuretics	-	-	-	-	5	6	5
Estrogens	-	-	10	35	5	18	-
Hypotensive agents	-	-	-	10	5	18	10
Progestins	-	-	-	10	-	12	-
Thyroid agents	-	-	-	-	10	12	5
Vasodilating drugs	-	-	-	-	10	41	10
Miscellaneous drugs	-	-	10	45	19	18	20
Unclassified therapeutic	-	-	-	5	9.5	-	-

a received by 18 adults, that is, 32% of the adults exhibited slight retinal signs of early ARM, such as 1 large druse > 63 μm in diameter, the presence of focal hyperpigmentation, or both. Previous work in our laboratory found a similar percentage of adults who did not have a diagnosis of ARM by a clinician, but who were classified by this macula grading system as presenting symptoms of early ARM (Jackson et al., in press). There are at least two possible explanations why 39% of the clinically normal adults were classified as having the earliest signs of ARM by the macula grading scale (grade 2). First, there are large variations in the definition of early ARM among clinicians

Table 7
Percentage of Subjects Taking Dietary Supplements with Age

	Age group						
Dietary supplement	20s	30s	40s	50s	60s	70s	80s
Calcium supplements	-	-	-	5	5	6	5
Cod liver oil	-	-	-	-	5	-	-
Magnesium supplements	-	-	-	-	5	-	-
Multivitamins	20	-	20	15	33	41	10
Potassium supplements	-	-	-	-	-	6	-
Vitamin A supplements	-	13	-	5	5	0	-
Vitamin B-6 supplements	-	-	-	-	5	0	-
Vitamin B-12 supplements	-	-	-	5	19	0	5
Vitamin C supplements	-	13	10	5	14	6	5
Vitamin E supplements	20	13	10	5	19	18	-
Zinc supplements	-	-	-	-	10	-	-

and grading scales (Bressler et al., 1988). Second, Curcio has suggested that a 63-μm-diameter drusen may be too small to accurately classify the subject as having early ARM (Curcio et al., in press). Curcio found that a cut-off of 125-μm-diameter drusen size more accurately correlates to the photoreceptor degeneration associated with the presence of ARM. Thus, the definition of early ARM used by the present study includes adults who do not yet have photoreceptor degeneration but whose fundi exhibit a characteristic of early ARM.

Obviously, one question is whether the aging-related decline in dark adaptation found on average in this study is because of the presence of pathology in the sample. Examining the adults over 60 years of age, the dark adaptation kinetics of the 18 adults receiving a grade of 2 were compared with the 28 adults receiving a grade of 0 or 1. No

differences between the two groups were found in the rod-cone break, second component, third component, rod break, time to baseline, or baseline sensitivity ($F[1, 44] = 0.62$, $p = 0.92$; $F[1, 44] = 0.81$, $p = 0.70$; $F[1, 44] = 0.05$, $p = 0.82$; $F[1, 44] = 0.62$, $p = 0.69$; $F[1, 44] = 3.71$, $p = 0.06$; $F[1, 44] = 0.16$, $p = 0.69$). Thus, it is clear that those adults with a grade of 2 are functionally similar to adults with a grade of 0 or 1 in regard to their dark adaptation parameters.

CONCLUSIONS

All of the measured dark adaptation parameters declined with age in adults of relatively good eye health. The rod-cone break, rod break, and time to baseline increased with age. Old adults in their 60s to 80s reached the rod-cone break about 2.1 min later than young adults in their 20s to 30s, and they required about 12 more mins to reach within 0.21 log unit of their baseline sensitivity compared with younger adults. The slope of the second and third components of dark adaptation decreased at a rate of 0.15 dB/decade and 0.05 dB/decade, respectively. Old adults exhibited a baseline sensitivity loss of 0.33 log unit after controlling for optical factors. This study did not specifically address the relationship between dark adaptation and difficulties encountered by old adults under dim illumination. However, the decreased rate of dark adaptation and decreased scotopic sensitivity exhibited by old adults may be part of the mechanism underlying their difficulty with activities at night and under dim illumination, an issue deserving of further study.

Although this study used improved methodology compared with the earlier work on dark adaptation and aging, it is of interest to compare the results of this study to the earlier literature. Contrary to the work of Birren and Shock (1950) and McFarland et al. (1960) who found that the rod-cone break did not change with age, this study found that the rod-cone break for adults in their 70s is delayed about 2.67 min compared with adults

in their 20s. Differences between the present study and the work of Birren and Shock and McFarland et al. may be because of methodological flaws in those studies. Birren and Shock's threshold sampling strategy was too infrequent. The dark adaptation data appear to have very few threshold measurements during the time that the rod-cone break becomes apparent. Birren and Shock reported a small increase in rod-cone break, but they discounted it because of the increased individual differences in the old adults' thresholds. McFarland et al. used a continuous, full-field bleaching light to achieve a full bleach. During bleaching, adults can experience discomfort from having to focus on a bright light and may have altered their fixation, which will produce inconsistent bleaching. McFarland et al.'s adults exhibited rod-cone break times of about 5 to 6 min, which are not consistent with other studies, including the present study. Using a full bleach and a similar stimulus, Hecht et al. (1937) found a rod-cone break of about 12 min for a full bleach.

McFarland et al.'s (1960) finding that the final dark-adapted sensitivity for the old adults was almost 2.0 log units less than young adults is about 4 times larger than reported in the aging and scotopic sensitivity literature (Jackson et al., in press; Sturr et al., 1997). Jackson et al. reported an uncorrected lens density sensitivity loss of 0.64 log unit, and Sturr et al. reported a loss of 0.69 log unit. Based on Birren et al.'s (1948) data, natural pupils could add as much as 0.5 log unit to the estimate, for a total sensitivity loss of 1.04 log units. For lens density to account for the remaining log unit of sensitivity loss, McFarland et al. on old adults would have to have exhibited an average LDI of over 3, suggesting the presence of severe cataracts. In comparison, an average LDI of 1.17 was

found in this study, and Jackson et al. reported an average LDI of 1.2. The presence of retinal pathology in McFarland et al.'s old adults may also account for their unusually high scotopic sensitivity loss, but the dark adaptation results are at odds with that conclusion. The presence of pathology dramatically alters the dark adaptation kinetics (Brown et al., 1986; Cideciyan et al., 1997; Jacobson et al., 1995), but they were not dramatically altered in McFarland et al. on data. In the end, it is difficult to know why the findings of McFarland et al.'s old adults showed large scotopic sensitivity loss, but these findings are important to emphasize that it is inconsistent with the other studies in this area.

Some of the previous literature is consistent with the findings of the present study. Holopigian et al. (1997) reported finding an aging-related increase in the rod-cone break. They reported that adults in their 80s exhibited an average rod-cone break 2.4 min longer than adults in their 20s. In comparison with Holopigian et al's adults, the adults in their 80s had an average rod-cone break 4.13 min longer than the adults in their 20s. Unfortunately, detailed information on the kinetics of dark adaptation were not reported in Holopigian et al., so further comparisons can not be made on the other dark adaptation parameters. Coile and Baker (1992) found an aging-related decrease in the rate of dark adaptation in cones, which was not examined in this study. Because rods appear more susceptible to the effects of age (Curcio et al., 1993) and disease (Curcio et al., 1996) than do cones, it would have been surprising to find that the rate of dark adaptation in rods is not affected in the present study.

The present study suggests that a portion of old adults scotopic impairment could be caused by alterations in rhodopsin regeneration. Certainly, these results do not rule out other mechanisms that may affect the overall level of scotopic sensitivity independent of the rate of dark adaptation such as rod photoreceptor density or post-receptoral structure and function. But the data presented here indicate for the first time in the literature that alterations in rhodopsin regeneration are a feasible candidate mechanism underlying aging-related scotopic sensitivity loss.

This study characterized old adults' macular health by using a grading scale. The macular grading scale employed in this study uses a definition of early ARM similar to that of the International Classification and Grading System for Age-related Maculopathy and Age-related Macular Degeneration (Bird et al., 1995). A permanent record of the visual appearance of the fundus on the day of psychophysical testing is useful for comparisons with other studies that use a macular grading system. Clinical evaluations can be arbitrary and variable among clinicians (Bressler et al., 1988). The slowing in the rate of dark adaptation presented in this study cannot be attributed to the presence of pathology in the sample. The photopic and scotopic visual sensitivity of the adults were comparable to previous studies in our laboratory that examined adults of excellent visual health (Jackson et al., in press; Jackson et al., 1997). Furthermore, adults who had no visible changes in the appearance of the macula associated with ARM (stage 0 or 1) exhibited a decreased rate of dark adaptation. Subjects with fundoscopic signs of early ARM were indistinguishable from adults without signs of early ARM in terms of

scotopic sensitivity and dark adaptation parameters. Clearly, the definition of early ARM used by this grading system needs further examination.

Although photoreceptor death has severe functional consequences on visual performance, it is possible that a decline in visual performance associated with ARM occurs before photoreceptor cell death is detectable. As mentioned earlier, Brown et al. (1986) demonstrated delayed dark adaptation kinetics in ARM patients in the absence of scotopic sensitivity loss and scotopic dysfunction that typifies photoreceptor loss. Thus, the measurement of dark adaptation appears more sensitive to the effects of ARM than the measurement of scotopic sensitivity (Chen et al., 1992; Jacobson et al., 1995; Steinmetz et al., 1993). Furthermore, Brown et al.'s findings suggest that functional measures of retinal health are at least as important as visual inspection of the retina in studying the earliest stages of ARM.

To test whether a functional definition of ARM is feasible, a longitudinal study examining adults at risk of developing ARM is necessary. Such a study should focus not only on fundoscopic signs and visual acuity, but also on functional parameters like dark adaptation. Documenting the progression of ARM in those adults who ultimately develop the later stages of the disease would be valuable in ascertaining the manifestation of the earliest symptoms presented by the disease. In the absence of a genetic test for ARM, this is possibly the most feasible approach to developing a clinical tool capable of early detection of the disease. Currently, the Age-Related Eye Disease Study (AREDS), sponsored by the National Eye Institute, is assessing the clinical course, and risk factors associated with AMD. Unfortunately, measurement of scotopic sensitivity and dark

adaptation is not included in AREDS. In fact, the only visual function assessed is visual acuity.

There are at least two possible explanations for the aging-related alterations in dark adaptation. The first view is that a biological aging process occurs in the retina that is distinct from ARM. The second explanation is that the aging-related decline in dark adaptation is actually produced by the same mechanisms that produce ARM. In this view, the biological mechanisms responsible for ARM may negatively impact rod function even if the subject is never diagnosed with ARM. Presently, it is difficult to determine which of the above two views is correct. To test the view that the biological mechanisms responsible for ARM and aging are the same, any treatment developed for ARM should retard or reverse the effects of aging. For example if vitamin A is impeded by Bruch's membrane in aging and ARM, megadoses of vitamin A should improve old adults' dark adaptation as well as ARM patients' dark adaptation. A study on the rate of progression of ARM similar to the AREDS study with a visual function battery that includes scotopic sensitivity and dark adaptation would help clarify the relationship between aging and ARM.

The aging-related decline in the rate of dark adaptation reported in the present study may be linked to old adults' subjective reports of difficulty with activities at night or their avoidance of those activities. While operating a vehicle at night, a person must navigate through a dynamic environment where ambient light levels may be continuously changing. Thus, old adults may experience difficulty driving at night because their sensitivity recovery is slowed, and the additional time required to adapt may not allow

the driver enough time to detect important environmental features. For example, if a person is bleached by oncoming vehicle lights or travels from a well-lit road to a darker-lit road, the driver may not be able to detect a pedestrian who is about to cross the road as quickly as would a young driver. Of course, driving a vehicle is not the only activity in which dark adaptation is important. In a person's home, navigating from a lit room to an unlit room may present visual difficulties that may result in a fall. McMurdo and Gaskell (1992) found a relationship between poor dark adaptation and falling in a nursing home population. Realistically, old adults do not experience the bleaching level or range of adaptation in every day life that are as extreme as those achieved in the present report, but the fact that cone-mediated and rod-mediated dark adaptation declines with age warrants a further examination of dark adaptation as a possible mechanism of old adults' night vision problems.

In summary, this study indicates that the rate of dark adaptation declines with age in adults that are classified as having good retinal health. As evidenced by a decreasing slope of the second component of dark adaptation, the rate of rhodopsin regeneration decreases with age. Older adults require significantly more time to reach the rod-cone break and baseline dark-adapted sensitivity. The aging-related slowing of the rate of dark adaptation was present even in those with no fundoscopic signs of ARM based on a macular grading system. This implies the existence of a biological change in rod phototransduction of the aged retina. Older adults exhibiting the earliest signs of ARM did not have greater scotopic sensitivity loss or slowed dark adaptation compared with those with no or minimal signs of ARM. Future work will examine the relationship

between the second component of dark adaptation and the dominant inactivation mechanism of the rod circulating current, and the suitability of dark adaptometry as a clinical tool in the investigation of early ARM.

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APPENDIX A

IRB APPROVAL FORM

OMB No. 0990-0020
Approved for use through 7/31/84

Protection of Human Subjects
Assurance Identification/Certification/Declaration
(Common Federal Rule)

POLICY: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See Section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the common rule.

Institutions with an assurance of compliance that covers the research to be conducted on file with the Department, Agency, or the Department of Health and Human Services (DHHS) should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency. Institutions which do not have such an assurance must submit an assurance and certification of IRB review and approval within 30 days of a written request from the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Application or Proposal Identification No. (if known)
☐ ORIGINAL	☐ GRANT ☐ CONTRACT ☐ FELLOWSHIP	
☐ FOLLOWUP	☐ COOPERATIVE AGREEMENT	
☐ EXEMPTION	☐ OTHER:	

4. Title of Application or Activity	5. Name of Principal Investigator, Program Director, Fellow, or Other
Night Vision Problems in Age-Related Macular Degeneration (Spatial Vision and Aging:Underlying Mechanisms)	Cynthia Owsley, Ph.D.

6. Assurance Status of this Project (Respond to one of the following)

☐ This Assurance, on file with the Department of Health and Human Services, covers this activity:

Assurance identification no. M- 1149 IRB identification no. 01NR

☐ This Assurance, on file with (agency/dept.) _____, covers this activity.

Assurance identification no. _____ IRB identification no. _____ (if applicable)

☐ No assurance has been filed for this project. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request

☐ Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101 (b), paragraph _____

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

☒ This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on (date) 12/30/97 by: ☐ Full IRB Review or ☒ Expedited Review.

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided.

10. Name and Address of Institution

The University of Alabama at Birmingham
1120A Administration Building
701 South 20th Street
Birmingham, AL 35294-0111

11. Phone No. (with area code)	12. Fax No. (with area code)
(205)934-3789	(205)975-5977

13. Name of Official	14. Title
Marilyn Doss, M.A.	Vice Chair-IRB

15. Signature	16. Date
Marilyn Doss	12/30/97

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OPTIONAL FORM 310 (6-92)
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APPENDIX B

DARK ADAPTATION MODELING PROGRAM

```
**********;
**** gerald mcgwin, jr. ****;
**** revised 5 march 98 ***;
**********;

data TEMP; set greg.dissdata;

/****** LIMIT INPUT DATASET HERE *****/;

        /*if id eq 1;*/

*****************************************;

proc sort data=TEMP out=unique (keep = id) nodupkey;
by id;
run;

data _null_;
 if 0 then set unique nobs=count;
 call symput('uni',count);
 stop;
run;

%macro procstep;

 %do i = 1 %to &uni;
 data _null_;
  set unique;
  if _n_ = &i then call symput('level',id);
 run;

 data tempdata;
   set TEMP;
  where id = &level;

xx_1 = max(x - 12.5, 0);
xx_2 = max(x - 30.0, 0);

proc univariate noprint; var y; output out=tss_temp mean=ave n=num; run;
data _null_; set tss_temp;
call symput('ave',put(ave,12.6));
call symput('num',put(num,12.6));
```

```
data aa; set tempdata;
temp = (y - &ave)**2;
proc univariate noprint; var temp; output out=tss sum=tss; run;

data _null_; set tss;
call  symput('tss',put(tss,8.6));

*******************************;

proc reg noprint data=tempdata outest=reg_est; model y = x xx_1 xx_2; run;

data _null_; set reg_est;

call  symput('b0',put(intercep,5.2));
call symput('b1',put(x,5.2));
call symput('b2',put(xx_1,5.2));
call symput('b3',put(xx_2,5.2));

proc nlin data=tempdata outest=nlin_est maxiter=200 /*method = dud*/ noprint;

parms a_3l = &b0 b_3l=&b1 c_3l=&b2 d_3l=&b3 knot1=12.5 knot2=30.0;

if x < knot1 then do;
model y = a_3l + b_3l*x; by id;
end;

if (x > knot1) and (x < knot2) then do;
model y = (a_3l + b_3l*x) + c_3l*(x-knot1); by id;
end;

else if (x > knot2) then do;
model y = ((a_3l + b_3l*x) + c_3l*(x-knot1)) + d_3l*(x-knot2); by id;
end;

/********* ALTERNATIVE APPROACH **************
parms b0 = &b0 b1=&b1 b2=&b2 b3=&b3 knot1=12.5 knot2=30.0;
xx_1 = max(x - knot1, 0);
xx_2 = max(x - knot2, 0);
model y = b0 + b1*x + b2*xx_1 + b3*xx_2; by id;
*********************************************/

data nlinest1; set nlin_est; if _type_ = "FINAL";
drop _name_ _iter_ _type_ _sse_;
```

```
slope1 = b_3l;
slope2 = b_3l+c_3l;
slope3 = b_3l+c_3l+d_3l;

r2_3l=1-(_sse_/&tss);
num = &num;

proc print noobs data=nlinest1; var id slope1--slope3 knot1 knot2 r2_3l num;

run;

data tempdata;
   set TEMP;
  where id = &level;

xx_1 = max(x - 2.0, 0);
xx_2 = max(x - 12.5, 0);
xx_3 = max(x - 30.0, 0);

*********************************;

proc reg noprint data=tempdata outest=reg_est; model y = x xx_1 xx_2 xx_3; run;

data _null_; set reg_est;

call  symput('b0',put(intercep,5.2));
call symput('b1',put(x,5.2));
call symput('b2',put(xx_1,5.2));
call symput('b3',put(xx_2,5.2));
call symput('b4',put(xx_3,5.2));

proc nlin data = tempdata outest=nlin_est maxiter=200 /*method = dud*/ noprint;

parms a_4l = &b0 b_4l=&b1 c_4l=&b2 d_4l=&b3 e_4l=&b4 knot1=2.0 knot2=12.5
knot3=30.0;

if x < knot1 then do;
model y = a_4l + b_4l*x; by id;
end;

if (x > knot1) and (x < knot2) then do;
model y = (a_4l + b_4l*x) + c_4l*(x-knot1); by id;
```

```
end;

else if (x > knot2) and (x < knot3) then do;
model y = ((a_4l + b_4l*x) + c_4l*(x-knot1)) + d_4l*(x-knot2); by id;
end;

else if (x > knot3) then do;
model y = (((a_4l + b_4l*x) + c_4l*(x-knot1)) + d_4l*(x-knot2)) +
e_4l*(x-knot3); by id;
end;

data nlinest1; set nlin_est; if _type_ = "FINAL";
drop _name_ _iter_ _type_ _sse_;

slope1 = b_4l;
slope2 = b_4l+c_4l;
slope3 = b_4l+c_4l+d_4l;
slope4 = b_4l+c_4l+d_4l+e_4l;

r2_4l=1-(_sse_/&tss);
num = &num;

proc print noobs data=nlinest1; var id slope1--slope4 knot1 knot2 knot3
r2_4l num;

run;


%end;

%mend;

%procstep;

run;
```

GRADUATE SCHOOL
UNIVERSITY OF ALABAMA AT BIRMINGHAM
DISSERTATION APPROVAL FORM
DOCTOR OF PHILOSOPHY

Name of Candidate Gregory R. Jackson

Major Subject Psychology

Title of Dissertation Aging and Dark Adaptation

I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this student are such that _he may be recommended for the degree of Doctor of Philosophy.

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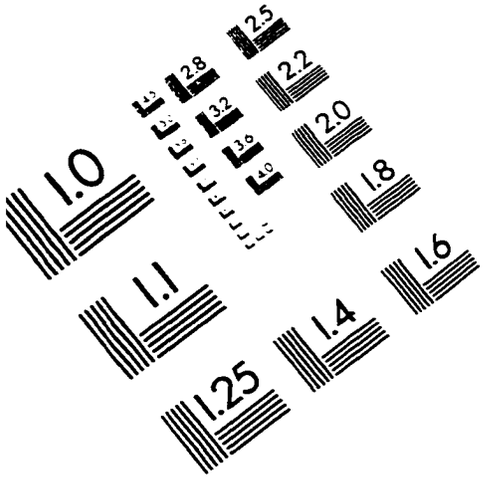

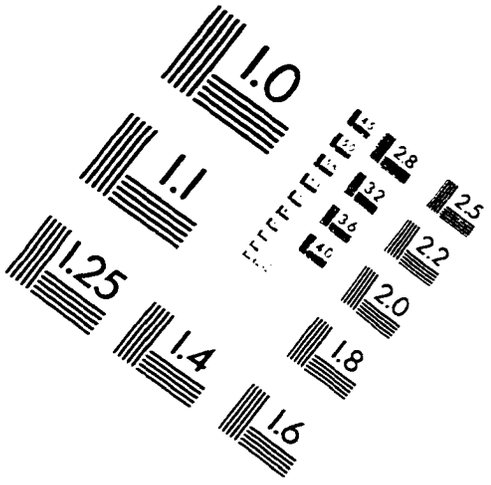

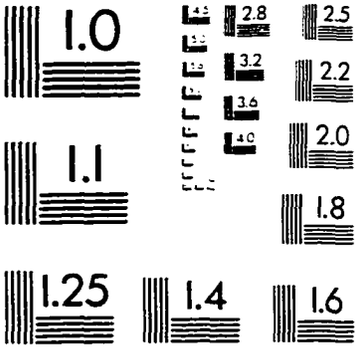

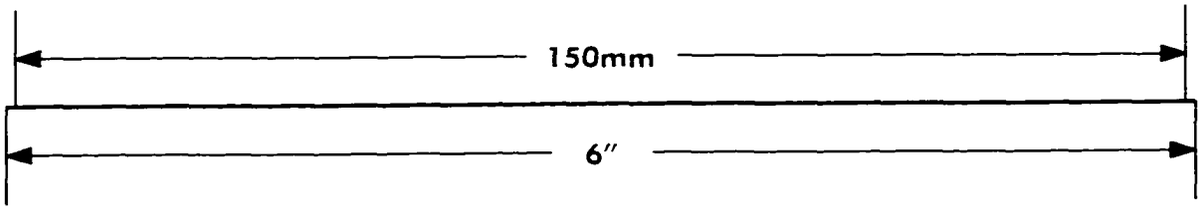

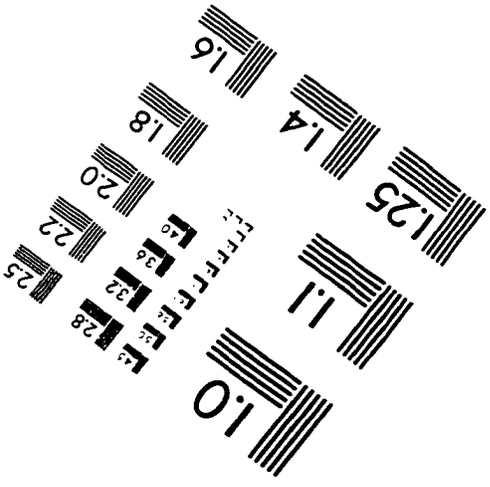

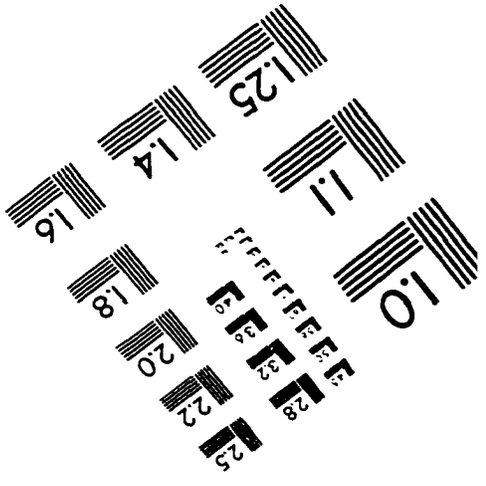

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